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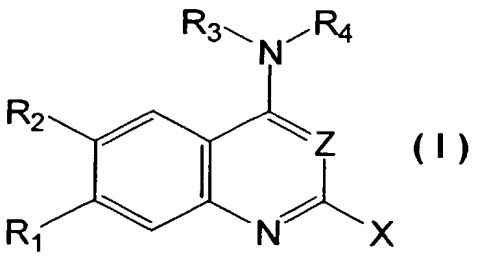
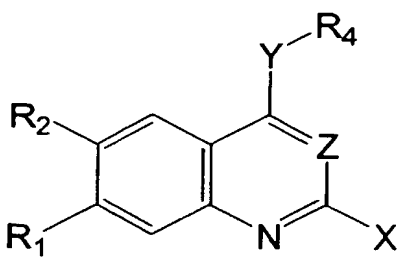
*[Continued on next page]*

(54) Title: QUINAZOLINE AND QUINOLINE DERIVATIVE COMPOUNDS AS INHIBITORS OF PROLYLPEPTIDASE, INDUCERS OF APOPTOSIS AND CANCER TREATMENT AGENTS




(I)




(II)

(57) Abstract: Quinazoline or quinoline derivatives of formula: (Formula I and II); wherein Z is CH or N; Y is O or S; X is $OR_5$ or $NR_5R_6$; $R_1$, $R_2$, $R_3$, $R_4$, $R_5$ and $R_6$ are as disclosed. Also described is a method for the inhibiting the prolyl peptidase, inducing apoptosis and treating cancer by administering a therapeutically effective amount of compounds of the formula (I) or (II).

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*GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

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# Quinazoline and Quinoline Derivative Compounds as Inhibitors of Prolylpeptidase, Inducers of Apoptosis and Cancer Treatment Agents

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## *DESCRIPTION OF THE INVENTION*

The present invention relates to:

(1) quinazoline and quinoline derivative compounds or purified stereoisomers or steroisomer mixtures of said compound and salts or prodrug forms thereof;

(2) pharmaceutical compositions comprising one or more of the compounds or purified stereoisomers or stereoisomer mixtures of the invention, or their salts or prodrugs forms thereof, with a pharmaceutically acceptable ingredient;

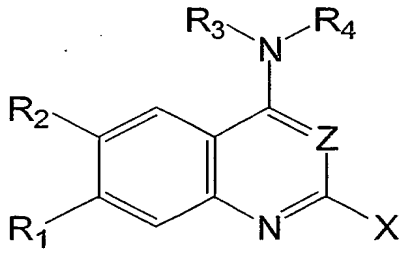
(3) methods of preparing the quinazoline and quinoline derivative compounds of (1); and

(4) methods for inhibiting prolylpeptidase, inducing apoptosis and treating cancer in mammals by administering an effective amount of (1) or (2) to a patient in need thereof.

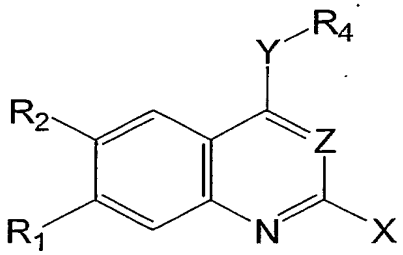
### *Description of the Compounds*

The compounds described as being part of the invention are novel quinazoline and quinoline derivative compounds which have the structural formula (I) or (II) defined below.

Embodiment 1:




or




(I) (II)

wherein,

Z is CH or N;

Y is O or S;

X is $OR_5$ or $NR_5R_6$;

$R_1$ and $R_2$ are independently selected from the group consisting of hydrogen, amino, cyano, halogen, hydroxy and nitro,

wherein $R_1$ and $R_2$ are both not hydrogen;

$R_3$ is selected from the group consisting of:

(a) hydrogen, and

(b) -($C_1$-$C_{10}$) linear or branched alkyl;

$R_4$ is -$(CH_2)_y$-$R_4$' wherein:

$R_4$' is selected from the group consisting of:

(a) -($C_1$-$C_5$) linear or branched alkyl optionally substituted with one to three substituents selected from the group consisting of:

(1) cyano,

(2) halogen,

(3) hydroxy,

(4) nitro,

(5) -($C_1$-$C_5$) linear or branched alkyl optionally substituted by halogen,

(6) -($C_1$-$C_5$) alkoxy-,

(7) -C(=O)$R_7$,

(8) -C(=O)O$R_7$,

(9) -C(=O)N$R_8R_9$,

(10) -S(=O)$R_{10}$, and

(11) -S(=O)$_2R_{10}$;

(b) -($C_3$-$C_8$) cycloalkyl,

(c) -($C_6$-$C_{10}$) aryl,

wherein (b) and (c) are optionally substituted with one to three substituents selected from the group consisting of

(1) amino,

(2) cyano,
(3) halogen,
(4) hydroxy,
(5) nitro,
(6) oxo,
(7) -($C_1$-$C_5$) linear or branched alkyl optionally substituted by halogen or hydroxy,
(8) -($C_1$-$C_5$) haloalkoxy-,
(9) -$(CH_2)_nC(=O)R_7$,
(10) -$(CH_2)_nC(=O)OR_7$,
(11) -$(CH_2)_nC(=O)C(=O)$-$OR_7$,
(12) -$(CH_2)_nC(=O)NR_8R_9$,
(13) -$S(=O)R_{10}$,
(14) -$S(=O)_2R_{10}$,
(15) -$C(=N$-$R_{10})$-($C_1$-$C_5$)-alkyl, and
(16) a saturated or unsaturated four to six membered heterocyclic ring containing one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring contains at least one carbon atom;

and

(d) a saturated or fully unsaturared four to six membered heterocyclic ring containing one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring contains at least one carbon atom and wherein said ring is optionally substituted with one to three substituents selected from the group consisting of amino, cyano, halogen, hydroxy, nitro, oxo, ($C_1$-$C_5$)-alkoxy, -$(CH_2)_nC(=O)OR_7$, -$(CH_2)_nC(=O)NR_8R_9$, -$S(=O)R_{10}$, -$S(=O)_2R_{10}$ and -($C_1$-$C_5$) linear or branched alkyl optionally substituted by halogen,

or

$R_3$ and $R_4$ form, together with the nitrogen to which they are attached, a saturated or fully unsaturated four to eight membered heterocyclic ring, wherein the nitrogen is the only heteroatom, which is optionally substituted with one to three substituents selected from the group consisting of amino, cyano, halogen, hydroxy, nitro, oxo, -($C_1$-$C_5$) alkoxy-, phenyl, -C(=O)$R_7$, -$(CH_2)_n$C(=O)$OR_7$, -$(CH_2)_n$C(=O)$NR_8R_9$, -S(=O)$R_{10}$, -$S(=O)_2R_{10}$ and -($C_1$-$C_5$) linear or branched alkyl optionally substituted by halogen;

$R_5$ has the formula -$(CHR_{11})_m$-A or -$(CHR_{11})_p$-O-A, where A is selected from the group consisting of:

(a) hydrogen,

(b) -($C_1$-$C_5$) linear or branched alkyl optionally substituted with cyano, halogen, hydroxy, -($C_1$-$C_5$) alkoxy- or -$NR_8R_9$,

(c) -($C_3$-$C_8$) cycloalkyl optionally substituted with cyano, halogen, hydroxy, -($C_1$-$C_5$) -alkyl, -($C_1$-$C_5$) alkoxy- or -$NR_8R_9$,

(d) -($C_6$-$C_{10}$) aryl optionally substituted with one to three substituents selected from the group consisting of:

(1) cyano,

(2) halogen,

(3) hydroxy,

(4) nitro,

(5) -$NR_8R_9$,

(6) -($C_1$-$C_5$) linear or branched alkyl optionally substituted with -$NR_8R_9$ or halogen,

(7) -($C_1$-$C_5$)-alkoxy wherein the alkyl is optionally substituted with -$NR_8R_9$ or halogen,

(8) -($C_6$-$C_{10}$) aryl-($C_1$-$C_5$)-alkoxy-

(9) -($C_6$-$C_{10}$) aryloxy optionally substituted with halogen,

(10) -($C_6$-$C_{10}$) -aryl optionally substituted with halogen,

(11) -$CH_2$-($C_6$-$C_{10}$)-aryl,

(12) -C(=O)$R_7$,

(13) -C(=O)$OR_7$,

(14) -C(=O)$NR_8R_9$,

(15) $-S(=O)R_{10}$,

(16) $-S(=O)_2R_{10}$, and

(17) a saturated or fully unsaturated four to eight membered heterocyclic ring containing one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring:

(a17) contains at least one carbon atom,

(b17) is directly linked to the $-(C_6-C_{10})$-aryl or is linked to the $-(C_6-C_{10})$-aryl via an -O- linkage, and

(c17) is optionally substituted with $-(C_1-C_5)$-alkyl, $-(CH_2)_nC(=O)OR_7$ or $-(CH_2)_nC(=O)NR_8R_9$,

(e) a saturated or fully unsaturated four to eight membered heterocyclic ring containing one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring contains at least one carbon atom, and is optionally substituted with

(1) $-(C_1-C_5)$-alkyl optionally substituted by halogen,

(2) phenyl optionally substituted by halogen,

(3) $-(C_1-C_5)$-alkoxy- wherein the alkyl is optionally substituted with halogen,

(4) $-(C_6-C_{10})$ aryloxy wherein the aryl is optionally substituted with halogen, or

(5) oxo,

and

(f) a fused bicyclo ring wherein one ring is a saturated or fully unsaturated five to six membered heterocyclic ring which contains one to three heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said heterocyclic ring contains at least one carbon atom, and the other ring is a saturated or fully unsaturated five to eight membered carbocycle,

$R_6$ is selected from the group consisting of:

(a) hydrogen, and

(b) -($C_1$-$C_5$) linear or branched alkyl,

wherein $R_5$ and $R_6$ are not both hydrogen;

or

$R_5$ and $R_6$ form, together with the nitrogen to which they are attached, a saturated or fully unsaturated four to eight membered heterocyclic ring, which optionally contains one to three additional nitrogen atoms wherein said ring contains at least one carbon atom, and wherein said ring is optionally substituted with one to three substituents selected from the group consisting of:

(a) amino,

(b) cyano,

(c) halogen,

(d) hydroxy,

(e) nitro,

(f) oxo,

(g) -($C_1$-$C_5$) linear or branched alkyl optionally substituted by halogen or -($C_1$-$C_5$) -alkoxy,

(h) -($C_1$-$C_5$) alkoxy,

(i) -($C_1$-$C_5$) alkoxy-($C_1$-$C_5$)-alkyl,

(j) -($C_6$-$C_{10}$) aryl optionally substituted by halogen or -($C_1$-$C_5$)-alkyl,

(k) -($C_1$-$C_5$)-alkyl-phenyl optionally substituted by halogen or -($C_1$-$C_5$)-alkyl,

(l) -$(CH_2)_nC(=O)OR_7$,

(m) -$(CH_2)_nC(=O)NR_8R_9$,

(n) -$(CH_2)_nNR_8R_9$,

(o) -$S(=O)R_{10}$,

(p) -$S(=O)_2R_{10}$, and

(q) -$(CH_2)_n$-Q, wherein Q is a saturated or fully unsaturated four to eight membered heterocyclic ring containing one to four nitrogens, wherein said ring contains at least one carbon atom;

wherein ($R_3$ and $R_4$) ≠ ($R_5$ and $R_6$) when:

(1) $R_3/R_4$ or $R_5/R_6$ contain an unsubstituted -$(CH_2)_n$-$C_6$-$C_{10}$-aryl substituent, or

(2) $R_3/R_4$ or $R_5/R_6$ form a heterocyclic ring;

$R_7$ is selected from the group consisting of hydrogen, -($C_1$-$C_5$) linear or branched alkyl, phenyl, -($C_1$-$C_5$)-alkyl-phenyl, and -($C_3$-$C_8$) cycloalkyl which are optionally substituted with one to three substituents selected from the group consisting of halogen, oxo, -($C_1$-$C_5$) alkoxy, -C(=O)$R_{11}$ and -($C_1$-$C_5$) linear or branched alkyl optionally substituted by halogen;

$R_8$ and $R_9$ are independently selected from the group consisting of:

(a) hydrogen,

(b) -($C_1$-$C_5$) linear or branched alkyl which is optionally substituted with a substituent selected from the group consisting of halogen and -($C_1$-$C_5$) alkoxy,

(c) -($C_1$-$C_5$) alkoxy,

(d) -($C_6$-$C_{10}$) aryl, and

(e) -$(CH_2)_n$-R wherein R is a five to six membered saturated or fully unsaturated heterocyclic ring containing one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring contains at least one carbon atom,

wherein (c)-(e) are optionally substituted with one to three substituents selected from the group consisting of halogen, -($C_1$-$C_5$) alkoxy, -C(=O)$R_7$ and -($C_1$-$C_5$) linear or branched alkyl optionally substituted by halogen,

or

$R_8$ and $R_9$ form, together with the nitrogen to which they are attached, a saturated or fully unsaturated four to eight membered heterocyclic ring, optionally containing one to three additional heteroatoms selected from the group consisting of nitrogen and

oxygen wherein said ring contains at least one carbon atom and wherein said heterocyclic ring is optionally substituted with -($C_1$-$C_5$) linear or branched alkyl;

$R_{10}$ is hydrogen, -$NR_8R_9$, -$OR_{11}$, -($C_1$-$C_5$) linear or branched alkyl, or phenyl;

each occurrence of $R_{11}$ is independently selected from the group consisting of hydrogen, -($C_1$-$C_5$) linear or branched alkyl and phenyl;

n, m and p are independently an integer from 0 - 3;

y is an integer from 0 - 2;

or a purified stereoisomer or stereoisomer mixture of said compound or a salt of said compound or purified stereoisomer or stereoisomer mixture thereof.

Embodiment 2

Also described are compounds of formula (I) or (II) wherein:

Z is CH or N;

Y is O or S;

X is $OR_5$ or $NR_5R_6$;

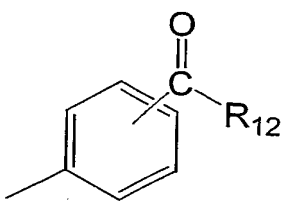
$R_1$ and $R_2$ are hydrogen;

$R_3$ is selected from the group consisting of:

(a) hydrogen, and

(b) -($C_1$-$C_5$) linear or branched alkyl;

$R_4$ is -$(CH_2)_yR_4'$, wherein

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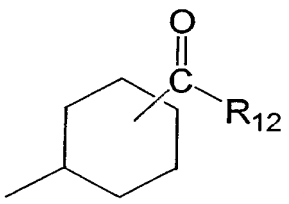



;

$R_4'$ is:

$R_5$ has the formula $-(CHR_{11})_m-A$ or $-(CHR_{11})_p-O-A$, where A is selected from the group consisting of:

(a) hydrogen,

(b) $-(C_1-C_5)$ linear or branched alkyl optionally substituted with cyano, halogen, hydroxy, $-(C_1-C_5)$ alkoxy or $-NR_8R_9$,

(c) $-(C_3-C_8)$ cycloalkyl optionally substituted with cyano, halogen, hydroxy, $-(C_1-C_5)$-alkyl, $-(C_1-C_5)$ alkoxy or $-NR_8R_9$,

(d) $-(C_6-C_{10})$ aryl optionally substituted with one to three substituents selected from the group consisting of:

(1) cyano,

(2) halogen,

(3) hydroxy,

(4) nitro,

(5) $-NR_8R_9$,

(6) $-(C_1-C_5)$-alkyl optionally substituted with halogen,

(7) $-(C_1-C_5)$-alkoxy wherein the alkyl is optionally substituted $-NR_8R_9$ or halogen,

(8) $-(C_6-C_{10})$-aryl-$(C_1-C_5)$-alkoxy

(9) $-(C_6-C_{10})$-aryloxy optionally substituted with halogen

(10) $-(C_6-C_{10})$-aryl optionally substituted with halogen,

(11) $-CH_2-(C_6-C_{10})$-aryl,

(12) $-C(=O)R_7$,

(13) $-C(=O)OR_7$,

(14) $-C(=O)NR_8R_9$,

(15) $-S(=O)R_{10}$;

(16) $-S(=O)_2R_{10}$; and

(17) a saturated or fully unsaturated four to eight membered heterocyclic ring containing one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring:

(a17) contains at least one carbon atom;

(b17) is directly linked to the $-(C_6-C_{10})$-aryl or is linked to the $-(C_6-C_{10})$-aryl via an -O- linkage; and

(c17) is optionally substituted with -($C_1$-$C_5$)-alkyl, -$(CH_2)_n$$COOR_7$ or -$(CH_2)_n$$CONR_8R_9$,

and

(e) a saturated or fully unsaturated four to eight membered heterocyclic ring containing one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring contains at least one carbon atom, and is optionally substituted with

(1) -($C_1$-$C_5$)-alkyl optionally substituted by halogen,

(2) phenyl optionally substituted by halogen,

(3) -($C_1$-$C_5$)-alkoxy- wherein the alkyl is optionally substituted with halogen,

(4) -($C_1$-$C_5$)-aryloxy- wherein the aryl is optionally substituted with halogen, or

(5) oxo;

$R_6$ is selected from the group consisting of:

(a) hydrogen, and

(b) -($C_1$-$C_5$) linear or branched alkyl,

wherein $R_5$ and $R_6$ are not both hydrogen;

$R_5$ and $R_6$ form, together with the nitrogen to which they are attached, a saturated or fully unsaturated four to eight membered heterocyclic ring, optionally containing one to three additional heteroatoms selected from the group consisting of nitrogen and oxygen wherein said ring contains at least one carbon atom wherein said heterocyclic ring is optionally substituted with -($C_1$-$C_5$) alkyl;

$R_7$ is selected from the group consisting of hydrogen, -($C_1$-$C_5$) linear or branched alkyl, phenyl, -($C_1$-$C_5$)-alkyl-phenyl, and -($C_3$-$C_8$) cycloalkyl which are optionally substituted with one to three substituents selected from the group

consisting of halogen, oxo, -($C_1$-$C_5$) alkoxy-, -C(=O)$R_7$ and -($C_1$-$C_5$) linear or branched alkyl optionally substituted by halogen;

$R_8$ and $R_9$ are independently selected from the group consisting of:

(a) hydrogen,

(b) -($C_1$-$C_5$) linear or branched alkyl, which is optionally substituted with a substituent selected from the group consisting of halogen and -($C_1$-$C_5$) alkoxy,

(c) -($C_1$-$C_5$) alkoxy,

(d) -($C_6$-$C_{10}$) aryl, and

(e) -$(CH_2)_n$-R wherein R is a saturated or fully unsaturated five to six membered heterocyclic ring containing one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring contains at least one carbon atom,

wherein (c)-(e) are optionally substituted with one to three substituents selected from the group consisting of halogen, -($C_1$-$C_5$) alkoxy- and -($C_1$-$C_5$) linear or branched alkyl optionally substituted by halogen;

$R_{10}$ is hydrogen, -$NR_8R_9$, -$OR_{11}$, -($C_1$-$C_5$) linear or branched alkyl, or phenyl;

each occurrence of $R_{11}$ is independently selected from the group consisting of hydrogen, -($C_1$-$C_5$) linear or branched alkyl and phenyl;

$R_{12}$ is -$R_{13}$, -$OR_{13}$, or -$NR_{14}R_{15}$;

$R_{13}$ is

(a) hydrogen,

(b) -($C_1$-$C_5$) linear or branched alkyl optionally substituted with halogen, or

(c) phenyl optionally substituted with halogen;

$R_{14}$ and $R_{15}$ are independently selected from the group consisting of:

(a) hydrogen,

(b) -($C_1$-$C_5$) linear or branched alkyl optionally substituted with halogen, and

(c) phenyl optionally substituted with halogen;

n, m and p are independently an integer from 0 - 3;

y is an integer from 0 - 2; and

y + (m + p) equals an integer from 1 - 8;

or a purified stereoisomer or stereoisomer mixture of said compound or a salt of said compound or purified stereoisomer or stereoisomer mixture thereof.

Embodiment 3

Also described are compounds with the formula (I) and (II) wherein:

Z is CH or N;

Y is O or S;

X is $OR_5$ or $NR_5R_6$;

$R_1$ and $R_2$ are independently selected from the group consisting of hydrogen and -$OCH_3$ wherein at least one of $R_1$ and $R_2$ is -$OCH_3$;

$R_3$ is hydrogen;

$R_4$ is -$(CH_2)_y$-$R_4$' wherein:

$R_4$' is selected from the group consisting of:

(a) -($C_1$-$C_5$) linear or branched alkyl which is optionally substituted with one to three substituents selected from the group consisting of:

(1) cyano,

(2) halogen,

(3) hydroxy,

(4) nitro,

(5) -($C_1$-$C_5$) linear or branched alkyl optionally substituted by halogen,

(6) -($C_1$-$C_5$) alkoxy,

(7) -C(=O)$R_7$,

(8) $-C(=O)OR_7$,

(9) $-C(=O)NR_8R_9$,

(10) $-S(=O)R_{10}$, and

(11) $-S(=O)_2R_{10}$,

(b) $-(C_3-C_8)$ cycloalkyl,

(c) $-(C_6-C_{10})$ aryl,

wherein (b) and (c) are optionally substituted with one to three substituents selected from the group consisting of

(1) amino,

(2) cyano,

(3) halogen,

(4) hydroxy,

(5) nitro,

(6) oxo,

(7) $-(C_1-C_5)$ linear or branched haloalkyl

(8) $-(C_1-C_5)$ haloalkoxy,

(9) $-(CH_2)_nC(=O)R_7$,

(10) $-(CH_2)_nC(=O)OR_7$,

(11) $-(CH_2)_nC(=O)C(=O)-OR_7$

(12) $-(CH_2)_nC(=O)NR_8R_9$,

(13) $-S(=O)R_{10}$,

(14) $-S(=O)_2R_{10}$;

(15) $-C(=N-R_{10})-(C_1-C_5)$ alkyl, and

(16) a saturated or unsaturated four to six membered heterocyclic ring containing one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur wherein said ring contains at least one carbon atom,

and

(d) a saturated or fully unsaturated four to eight membered heterocyclic ring containing one to four heteroatoms selected from the group

consisting of nitrogen, oxygen and sulfur, wherein said ring contains at least one carbon atom and wherein said ring is optionally substituted with one to three substituents selected from the group consisting of amino, cyano, halogen, hydroxy, nitro, oxo, -($C_1$-$C_5$) alkoxy, -$(CH_2)_nC(=O)OR_7$, -$(CH_2)_nC(=O)NR_8R_9$, -$S(=O)R_{10}$, -$S(=O)_2R_{10}$ and -($C_1$-$C_5$) linear or branched alkyl optionally substituted by halogen;

or

$R_3$ and $R_4$ form, together with the nitrogen to which they are attached, a saturated or fully unsaturated four to eight membered heterocyclic ring, wherein the nitrogen is the only heteroatom, which is optionally substituted with one to three substituents selected from the group consisting of amino, cyano, halogen, hydroxy, nitro, oxo, -($C_6$-$C_{10}$)-aryl, -$C(=O)R_7$, -$(CH_2)_nC(=O)OR_7$, -$(CH_2)_nC(=O)NR_8R_9$, -$S(=O)R_{10}$, -$S(=O)_2R_{10}$ and -($C_1$-$C_5$) linear or branched alkyl optionally substituted by halogen;

$R_5$ has the formula:

-$(CH_2)_p$-O-A where A is selected from the group consisting of:

(a) hydrogen,

(b) -($C_1$-$C_5$) linear or branched alkyl, optionally substituted with cyano, halogen, hydroxy, -($C_1$-$C_5$) alkoxy- or -$NR_8R_9$, and

(c) -($C_3$-$C_8$) cycloalkyl, optionally substituted with cyano, halogen, hydroxy, -($C_1$-$C_5$)-alkyl, -($C_1$-$C_5$) alkoxy or -$NR_8R_9$;

(d) -($C_6$-$C_{10}$)-aryl, optionally substituted with one to three substituents selected from the group consisting of:

(1) cyano,

(2) halogen,

(3) hydroxy,

(4) nitro,

(5) -$NR_8R_9$,

(6) -($C_1$-$C_5$)-alkyl optionally substituted with halogen,

(7) $(C_1-C_5)$-alkoxy wherein the alkyl is optionally substituted with $-NR_8R_9$ or halogen,

(8) $-(C_6-C_{10})$-aryl-$(C_1-C_5)$ alkoxy

(9) $-(C_6-C_{10})$-aryloxy optionally substituted with halogen,

(10) $-(C_6-C_{10})$-aryl optionally substituted with halogen,

(11) $-CH_2-(C_6-C_{10})$-aryl,

(12) $-C(=O)R_7$,

(13) $-C(=O)OR_7$,

(14) $-C(=O)NR_8R_9$,

(15) $-S(=O)R_{10}$;

(16) $-S(=O)_2R_{10}$; and

(17) a saturated or fully unsaturated four to eight membered heterocyclic ring containing one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring:

(a17) contains at least one carbon atom;

(b17) is directly linked to the $-(C_6-C_{10})$-aryl or is linked to the $-(C_6-C_{10})$-aryl via an -O- linkage, and

(c17) is optionally substituted with $-(C_1-C_5)$-alkyl, $-(CH_2)_nCOOR_7$ or $-(CH_2)_nCONR_8R_9$,

(e) a saturated or fully unsaturated four to eight membered heterocyclic ring containing one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring contains at least one carbon atom, and is optionally substituted with

(1) $-(C_1-C_5)$ alkyl optionally substituted by halogen,

(2) $-(C_6-C_{10})$-aryl optionally substituted by halogen,

(3) $-(C_1-C_5)$-alkoxy wherein the alkyl is optionally substituted with halogen,

(4) $-(C_1-C_5)$-aryloxy wherein the aryl is optionally substituted with halogen, or

(5) oxo,

and

(f) a fused bicyclo ring wherein one ring is a saturated or fully unsaturated five to six membered heterocyclic ring which contains one to three heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said heterocyclic ring contains at least one carbon and the other ring is a saturated or fully unsaturated five to eight membered carbocycle,

or

$-(CH_2)_m-A$ where A is selected from the group consisting of:

(a) hydrogen,

(b) $-(C_1-C_5)$ linear or branched alkyl optionally substituted with cyano, halogen, hydroxy, $-(C_1-C_5)$ alkoxy or $-NR_8R_9$,

(c) $-(C_3-C_8)$ cycloalkyl optionally substituted with cyano, halogen, hydroxy, $-(C_1-C_5)$-alkyl, $-(C_1-C_5)$ alkoxy or $-NR_8R_9$,

(d) $-(C_6-C_{10})$ aryl, optionally substituted with one to three substituents selected from the group consisting of:

(1) cyano,

(2) halogen,

(3) hydroxy,

(4) nitro,

(5) $-NR_8R_9$,

(6) $-(C_1-C_5)$ alkyl optionally substituted with halogen,

(7) $-(C_1-C_5)$ alkoxy wherein the alkyl is optionally substituted with $-NR_8R_9$ or halogen,

(8) $-C(=O)R_7$,

(9) $-C(=O)OR_7$,

(10) $-C(=O)NR_8R_9$,

(11) $-S(=O)R_{10}$;

(12) $-S(=O)_2R_{10}$; and

(13) a saturated or fully unsaturated four to eight membered heterocyclic ring containing one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring:

(a13) contains at least one carbon atom;

(b13) is directly linked to the -($C_6$-$C_{10}$) aryl or is linked to the -($C_6$-$C_{10}$) aryl via an -O- linkage, and

(c13) is optionally substituted with -($C_1$-$C_5$)-alkyl, -$(CH_2)_nC(=O)OR_7$ or -$(CH_2)_nC(=O)NR_8R_9$,

(e) a saturated or fully unsaturated four to eight membered heterocyclic ring containing one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring contains at least one carbon atom, and is optionally substituted with

(1) -($C_1$-$C_5$)-alkyl optionally substituted by halogen,

(2) phenyl optionally substituted by halogen,

(3) -($C_1$-$C_5$)-alkoxy wherein the alkyl is optionally substituted with halogen,

(4) -($C_1$-$C_5$)-aryloxy wherein the aryl is optionally substituted with halogen, or

(5) oxo,

and

(f) a fused bicyclo ring wherein one ring is a saturated or fully unsaturated five to six membered heterocyclic ring which contains one to three heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said heterocyclic ring contains at least one carbon atom and the other ring is a saturated or fully unsaturated five to eight membered carbocycle;

$R_6$ is selected from the group consisting of:

(a) hydrogen, and

(b) -($C_1$-$C_5$) linear or branched alkyl,

wherein $R_5$ and $R_6$ are not both hydrogen;

or

$R_5$ and $R_6$ form, together with the nitrogen to which they are attached, a saturated or fully unsaturated four to eight membered heterocyclic ring, which optionally contains one to three additional heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur wherein said ring contains at least one carbon atom, and wherein said ring is optionally substituted with one to three substituents selected from the group consisting of:

(a) amino,

(b) cyano,

(c) halogen,

(d) hydroxy,

(e) nitro,

(f) oxo,

(g) -($C_1$-$C_5$) linear or branched alkyl optionally substituted by halogen or -($C_1$-$C_5$) alkoxy,

(j) -($C_6$-$C_{10}$)-aryl optionally substituted by halogen or -($C_1$-$C_5$)-alkyl,

(k) -($C_1$-$C_5$)-alkyl-phenyl optionally substituted by halogen or -($C_1$-$C_5$) alkyl,

(l) -$(CH_2)_nCOOR_7$,

(m) -$(CH_2)_nCONR_8R_9$,

(n) -$(CH_2)_nNR_8R_9$,

(o) -$S(=O)R_{10}$,

(p) -$S(=O)_2R_{10}$, and

(q) -$(CH_2)_n$-Q, wherein Q is:

(q1) a four to eight membered saturated or fully unsaturated heterocyclic ring containing one to four nitrogens, wherein said ring contains at least one carbon atom, or

(q2) -$C_6$-$C_{10}$-aryl optionally substituted with halogen or -($C_1$-$C_5$) alkyl;

wherein,

(i) $R_3 \neq R_4$,

(ii) $R_5 \neq R_6$, and

(iii) ($R_3$ and $R_4$) $\neq$ ($R_5$ and $R_6$)

$R_7$ is selected from the group consisting of hydrogen, -($C_1$-$C_5$) linear or branched alkyl, phenyl, -($C_1$-$C_5$)-alkyl-phenyl, and ($C_3$-$C_{10}$) cycloalkyl which are optionally substituted with one to three substituents selected from the group consisting of halogen, oxo, -($C_1$-$C_5$) alkoxy, -$(CH_2)_nC(=O)R_{11}$, -$(CH_2)_nC(=O)OR_{11}$, -$(CH_2)_nC(=O)NR_8R_9$, -$S(=O)R_{10}$, -$S(=O)_2R_{10}$ and -($C_1$-$C_5$) linear or branched alkyl optionally substituted by halogen;

$R_8$ and $R_9$ are independently selected from the group consisting of hydrogen, -($C_1$-$C_5$) linear or branched alkyl, -($C_1$-$C_5$) alkoxy or –($C_6$-$C_{10}$) aryl which is optionally substituted with one to three substituents selected from the group consisting of halogen, -($C_1$-$C_5$) alkoxy, -($C_1$-$C_5$) alkylamino, -$(CH_2)_nC(=O)R_7$, -$(CH_2)_nC(=O)OR_7$, -$(CH_2)_nC(=O)NR_8R_9$, -$S(=O)R_{10}$, -$S(=O)_2R_{10}$ and -($C_1$-$C_5$) linear or branched alkyl optionally substituted by halogen; or

$R_8$ and $R_9$ form, together with the nitrogen to which they are attached, a saturated or fully unsaturated, four to eight membered heterocyclic ring, wherein said ring has one to three additional heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur wherein said ring contains at least one carbon atom and wherein said heterocyclic ring is optionally substituted with -($C_1$-$C_5$) linear or branched alkyl;

$R_{10}$ is hydrogen, -$NR_8R_9$, -$OR_{11}$, -($C_1$-$C_5$) linear or branched alkyl, or phenyl;

$R_{11}$ is hydrogen, -($C_1$-$C_5$) linear or branched alkyl, or phenyl;

n, m and p are independently an integer from 0 - 3; and

y is an integer from 0 - 2,

or a purified stereoisomer or stereoisomer mixture of said compound or a salt of said compound or purified stereoisomer or stereoisomer mixture thereof.

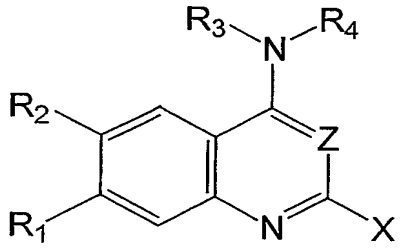
Pharmaceutically acceptable salts of these compounds as well as commonly used prodrugs of these compounds are also within the scope of the invention.

Detailed Description

Embodiment 1, preferred compounds

The preferred compounds of embodiment 1 have general formula (I) and are further defined below. In the following description of these preferred compounds, the definitions for the various groups and variables represent the preferred definitions when they differ from those of embodiment 1 as broadly defined above, and are to be understood as independent of each other.

The preferred compounds of embodiment 1 have the formula (I)



(I)

wherein

Z is N;

X is $OR_5$ or $NR_5R_6$ ;

$R_1$ and $R_2$ are independently selected from the group consisting of hydrogen, cyano, halogen, and hydroxy, and wherein $R_1$ and $R_2$ are both not hydrogen;

$R_3$ is selected from the group consisting of:

(a) hydrogen, and

(b) -($C_1$-$C_5$) linear or branched alkyl;

$R_4$ is -$(CH_2)_y$-$R_4$' wherein:

$R_4$' is selected from the group consisting of:

(a) -($C_1$-$C_5$) linear or branched alkyl optionally substituted with one to three substituents selected from the group consisting of:

(1) -C(=O)$R_7$,

(2) -C(=O)O$R_7$,

(3) -C(=O)N$R_8R_9$,

(4) -S(=O)$R_{10}$, and

(5) -$S(=O)_2R_{10}$;

(b) -($C_3$-$C_8$) cycloalkyl,

(c) -($C_6$-$C_{10}$) aryl,

wherein (b) and (c) are optionally substituted with one to three substituents selected from the group consisting of

(1) cyano,

(2) halogen,

(3) -$(CH_2)_n$C(=O)$R_7$,

(4) -$(CH_2)_n$C(=O)O$R_7$,

(5) -$(CH_2)_n$C(=O)C(=O)-O$R_7$,

(6) -$(CH_2)_n$C(=O)N$R_8R_9$,

(7) -S(=O)$R_{10}$,

(8) -$S(=O)_2R_{10}$,

(9) -C(=N-$R_{10}$)-($C_1$-$C_5$)-alkyl, and

(10) a saturated or unsaturated four to six membered heterocyclic ring containing one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring contains at least one carbon atom;

and

(d) a saturated or fully unsaturared four to six membered heterocyclic ring containing one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring contains at least one carbon atom and wherein said ring is optionally substituted with one to three substituents selected from the group consisting of amino, cyano, halogen, hydroxy, nitro, oxo, -($C_1$-$C_5$)-alkoxy, -$(CH_2)_nC(=O)OR_7$, -$(CH_2)_nC(=O)NR_8R_9$, -$S(=O)R_{10}$, -$S(=O)_2R_{10}$ and –($C_1$-$C_5$) linear or branched alkyl optionally substituted by halogen,

or

$R_3$ and $R_4$ form, together with the nitrogen to which they are attached, a saturated four to eight membered heterocyclic ring, wherein the nitrogen is the only heteroatom, which is optionally substituted with one substituent selected from the group consisting of -($C_1$-$C_5$) alkoxy, -$(CH_2)_nC(=O)OR_7$, and –($C_1$-$C_5$) linear or branched alkyl optionally substituted by halogen;

$R_5$ has the formula -$(CHR_{11})_m$-A or -$(CHR_{11})_p$-O-A, wherein $R_{11}$ is H and A is selected from the group consisting of:

(a) hydrogen,

(b) -($C_1$-$C_5$) linear or branched alkyl optionally substituted with halogen, -($C_1$-$C_5$) alkoxy or -$NR_8R_9$,

(c) -($C_6$-$C_{10}$) aryl optionally substituted with one to three substituents selected from the group consisting of:

(1) halogen,

(2) nitro,

(3) -($C_1$-$C_5$)-alkoxy wherein the alkyl is optionally substituted with -$NR_8R_9$ or halogen,

(4) -$CH_2$-phenyl,

(5) -$C(=O)R_7$,

(6) $-C(=O)OR_7$,

(7) $-C(=O)NR_8R_9$,

(8) $-S(=O)R_{10}$,

(9) $-S(=O)_2R_{10}$, and

(10) a saturated or fully unsaturated four to eight membered heterocyclic ring containing one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring:

(a10) contains at least one carbon atom,

(b10) is directly linked to the $-(C_6-C_{10})$-aryl or is linked to the $-(C_6-C_{10})$-aryl via an -O- linkage, and

(c10) is optionally substituted with $-(C_1-C_5)$-alkyl, $-(CH_2)_nC(=O)OR_7$ or $-(CH_2)_nC(=O)NR_8R_9$,

(d) a saturated or fully unsaturated five or six membered heterocyclic ring containing one to two heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring contains at least one carbon atom, and is optionally substituted with oxo;

and

(e) a fused bicyclo ring wherein one ring is a saturated or fully unsaturated five to six membered heterocyclic ring which contains one to three heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said heterocyclic ring contains at least one carbon atom, and the other ring is a saturated five to six membered carbocycle,

$R_6$ is selected from the group consisting of:

(a) hydrogen, and

(b) $-(C_1-C_5)$ linear or branched alkyl,

wherein $R_5$ and $R_6$ are not both hydrogen;

or

$R_5$ and $R_6$ form, together with the nitrogen to which they are attached, a saturated five to seven membered heterocyclic ring, which optionally contains one additional nitrogen atom, and wherein said ring is optionally substituted with one to three substituents selected from the group consisting of:

(a) halogen,

(b) oxo,

(c) -($C_1$-$C_5$) linear or branched alkyl optionally substituted by halogen or -($C_1$-$C_5$)-alkoxy,

(d) -($C_1$-$C_5$) alkoxy,

(e) -$(CH_2)_nC(=O)OR_7$,

(f) -$(CH_2)_nC(=O)NR_8R_9$, and

(g) -$(CH_2)_n$-Q, wherein Q is a pyridyl group;

wherein ($R_3$ and $R_4$) ≠ ($R_5$ and $R_6$) when:

(1) $R_3/R_4$ or $R_5/R_6$ contain an unsubstituted -$(CH_2)_n$-$C_6$-$C_{10}$-aryl substituent, or

(2) $R_3/R_4$ or $R_5/R_6$ form a heterocyclic ring;

$R_7$ is selected from the group consisting of hydrogen, -($C_1$-$C_5$) linear or branched alkyl, and phenyl, which are optionally substituted with one to three substituents selected from the group consisting of halogen, oxo, -($C_1$-$C_5$) alkoxy, and –($C_1$-$C_5$) linear or branched alkyl optionally substituted by halogen;

$R_8$ and $R_9$ are independently selected from the group consisting of:

(a) hydrogen,

(b) -($C_1$-$C_5$) linear or branched alkyl which is optionally substituted with a substituent selected from the group consisting of halogen and -($C_1$-$C_5$) alkoxy,

(c) -($C_6$-$C_{10}$) aryl, and

wherein (c) is optionally substituted with one to three substituents selected from the group consisting of halogen, -($C_1$-$C_5$) alkoxy, and -($C_1$-$C_5$) linear or branched alkyl optionally substituted by halogen,

or

$R_8$ and $R_9$ form, together with the nitrogen to which they are attached, a saturated or fully unsaturated five or six membered heterocyclic ring, optionally containing one to two additional heteroatoms selected from the group consisting of nitrogen and oxygen;

$R_{10}$ is hydrogen, -$NR_8R_9$, -$OR_{11}$, -($C_1$-$C_5$) linear or branched alkyl, or phenyl;

except in the definition of $R_5$ , each occurrence of $R_{11}$ is independently selected from the group consisting of hydrogen and –($C_1$-$C_5$) linear or branched alkyl and phenyl;

n, m and p are independently an integer from 0 - 3;

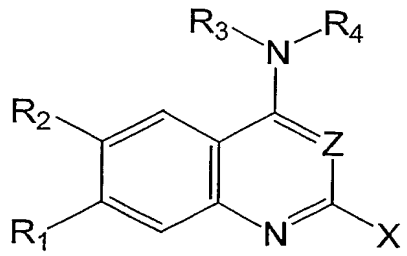
y is an integer from 0 - 2;

or a purified stereoisomer or stereoisomer mixture of said compound or a salt of said compound or purified stereoisomer or stereoisomer mixture thereof.

Embodiment 1, more preferred compounds

The more preferred compounds of embodiment 1 have general formula (I) and are further defined below. In the following description of these more preferred compounds, the definitions for the various groups and variables represent the more preferred definitions when they differ from those of embodiment 1 as broadly defined above, and are to be understood as independent of each other.

The more preferred compounds of embodiment 1 have the formula (I)



(I)

wherein,

Z is N,

X is $NR_5R_6$;

$R_1$ and $R_2$ are independently selected from the group consisting of hydrogen and halogen, wherein $R_1$ and $R_2$ are both not hydrogen;

$R_3$ is hydrogen,

$R_4$ is $-(CH_2)_y-R_4'$ wherein:

$R_4'$ is selected from the group consisting of:

(a) cyclohexyl,

(b) -phenyl,

wherein (a) and (b) are optionally substituted with one to three substituents selected from the group consisting of

(1) $-(CH_2)_nC(=O)R_7$,

(2) $-(CH_2)_nC(=O)OR_7$,

(3) $-(CH_2)_nC(=O)NR_8R_9$,

(4) $-S(=O)R_{10}$,

(5) $-S(=O)_2R_{10}$,

(6) $-C(=N-R_{10})-(C_1-C_5)$-alkyl, and

(7) a saturated or fully unsaturated six membered heterocyclic ring containing one to two heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur,

and

(d) a fully unsaturated five membered heterocyclic ring containing one heteroatom selected from the group consisting of oxygen and sulfur, wherein said ring is optionally substituted with one substituent selected from the group consisting of

$-(CH_2)_nC(=O)OR_7$, $-(CH_2)_nC(=O)NR_8R_9$, $-S(=O)R_{10}$, and $-S(=O)_2R_{10}$,

or

$R_3$ and $R_4$ form, together with the nitrogen to which they are attached, a saturated six membered heterocyclic ring, wherein the nitrogen is the only heteroatom,

$R_5$ has the formula $-(CHR_{11})_m$-A or $-(CHR_{11})_p$-O-A, wherein $R_{11}$ is H and A is selected from the group consisting of:

(a) $-(C_1-C_5)$ linear or branched alkyl optionally substituted with $-(C_1-C_5)$ alkoxy,

(b) -phenyl optionally substituted with one to two substituents selected from the group consisting of:

(1) halogen,

(2) $-(C_1-C_5)$-alkoxy

(3) $-C(=O)OR_7$,

(4) $-C(=O)NR_8R_9$,

(5) morpholinyl

(c) a saturated or fully unsaturated five or six membered heterocyclic ring containing one to two heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring is optionally substituted with oxo,

(d) a fused bicyclo ring wherein one ring is a saturated or fully unsaturated five to six membered heterocyclic ring which contains one to two heteroatoms selected from the group consisting of nitrogen and oxygen, wherein said heterocyclic ring contains at least one carbon atom, and the other ring is a saturated or fully unsaturated five to six membered carbocycle;

$R_6$ is hydrogen,

or

$R_5$ and $R_6$ form, together with the nitrogen to which they are attached, a fully saturated five or six membered heterocyclic ring, which optionally contains one additional nitrogen atom, and wherein said ring is optionally substituted with one to two substituents selected from the group consisting of:

(a) -($C_1$-$C_5$) linear or branched alkyl optionally substituted by halogen or -($C_1$-$C_5$)-alkoxy,

(b) -$(CH_2)_nC(=O)OR_7$, and

(c) -$(CH_2)_nC(=O)NR_8R_9$,

wherein ($R_3$ and $R_4$) ≠ ($R_5$ and $R_6$) when:

(1) $R_3/R_4$ or $R_5/R_6$ contain an unsubstituted -$(CH_2)_n$-$C_6$-$C_{10}$-aryl substituent, or

(2) $R_3/R_4$ or $R_5/R_6$ form a heterocyclic ring;

$R_7$ is selected from the group consisting of hydrogen, -($C_1$-$C_5$) linear or branched alkyl and phenyl, which are optionally substituted with one halogen,

$R_8$ and $R_9$ are independently selected from the group consisting of:

(a) hydrogen,

(b) -($C_1$-$C_5$) linear or branched alkyl, and

(c) -phenyl, and

wherein (c) is optionally substituted with one substituent selected from the group consisting of halogen and -($C_1$-$C_5$) alkoxy,

$R_{10}$ is -$NR_8R_9$ or -$OR_{11}$ ,

each occurrence of $R_{11}$ is hydrogen,

n, m and p are independently an integer from 0 - 3;

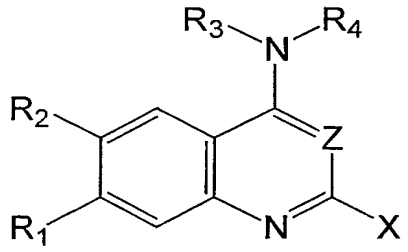
y is an integer from 0 - 2;

or a purified stereoisomer or stereoisomer mixture of said compound or a salt of said compound or purified stereoisomer or stereoisomer mixture thereof.

Embodiment 2, preferred compounds

The preferred compounds of embodiment 2 have general formula (I) and are further defined below. In the following description of these preferred compounds, the definitions for the various groups and variables represent the preferred definitions when they differ from those of embodiment 2 as broadly defined above, and are to be understood as independent of each other.

The preferred compounds of embodiment 2 have the formula (I)



(I)

wherein:

Z is N;

X is $OR_5$ or $NR_5R_6$;

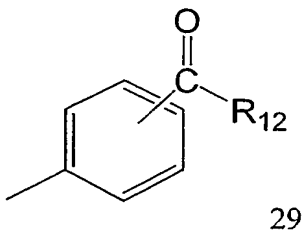
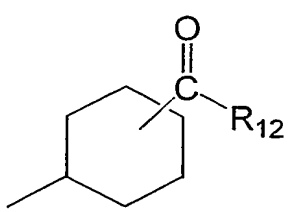
$R_1$ and $R_2$ are hydrogen;

$R_3$ is selected from the group consisting of:

(a) hydrogen, and

(b) -($C_1$-$C_5$) linear or branched alkyl;

$R_4$ is -$(CH_2)_yR_4'$, wherein

 or  ;

$R_4'$ is:

$R_5$ has the formula $-(CHR_{11})_m-A$ or $-(CHR_{11})_p-O-A$, wherein $R_{11}$ is H and A is selected from the group consisting of:

(a) hydrogen,

(b) $-(C_1-C_5)$ linear or branched alkyl optionally substituted with halogen, $-(C_1-C_5)$ alkoxy or $-NR_8R_9$,

(c) $-(C_6-C_{10})$-aryl optionally substituted with one to three substituents selected from the group consisting of:

(1) halogen,

(2) nitro,

(3) $-(C_1-C_5)$-alkoxy wherein the alkyl is optionally substituted with $-NR_8R_9$ or halogen,

(4) $CH_2$-phenyl,

(5) $-C(=O)R_7$,

(6) $-C(=O)OR_7$,

(7) $-C(=O)NR_8R_9$,

(8) $-S(=O)R_{10}$;

(9) $-S(=O)_2R_{10}$; and

(10) a saturated or fully unsaturated four to eight membered heterocyclic ring containing one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring:

(a10) contains at least one carbon atom;

(b10) is directly linked to the $-(C_6-C_{10})$-aryl or is linked to the $-(C_6-C_{10})$-aryl via an -O- linkage; and

(c10) is optionally substituted with $-(C_1-C_5)$-alkyl, $-(CH_2)_nCOOR_7$ or $-(CH_2)_nCONR_8R_9$,

and

(d) a saturated or fully unsaturated five to six membered heterocyclic ring containing one to two heteroatoms selected from the group consisting

of nitrogen, oxygen and sulfur, wherein said ring contains at least one carbon atom, and is optionally substituted with oxo,

$R_6$ is selected from the group consisting of:

(a) hydrogen, and

(b) -($C_1$-$C_5$) linear or branched alkyl,

wherein $R_5$ and $R_6$ are not both hydrogen;

or

$R_5$ and $R_6$ form, together with the nitrogen to which they are attached, a saturated five to seven membered heterocyclic ring, optionally containing one additional heteroatom selected from the group consisting of nitrogen and oxygen wherein said heterocyclic ring is optionally substituted with –($C_1$-$C_5$)-alkyl;

$R_7$ is selected from the group consisting of hydrogen, -($C_1$-$C_5$) linear or branched alkyl and phenyl, which are optionally substituted with one to three substituents selected from the group consisting of halogen, oxo, -($C_1$-$C_5$) alkoxy-, and –($C_1$-$C_5$) linear or branched alkyl optionally substituted by halogen;

$R_8$ and $R_9$ are independently selected from the group consisting of:

(a) hydrogen,

(b) -($C_1$-$C_5$) linear or branched alkyl, which is optionally substituted with a substituent selected from the group consisting of halogen and ($C_1$-$C_5$) alkoxy-,

(c) -($C_6$-$C_{10}$) aryl, and

wherein (c) is optionally substituted with one to three substituents selected from the group consisting of halogen,-($C_1$-$C_5$) alkoxy and –($C_1$-$C_5$) linear or branched alkyl optionally substituted by halogen;

$R_{10}$ is hydrogen, -$NR_8R_9$, -$OR_{11}$, -($C_1$-$C_5$) linear or branched alkyl, or phenyl;

each occurrence of $R_{11}$ is independently selected from the group consisting of hydrogen and -($C_1$-$C_5$) linear or branched alkyl and phenyl;

$R_{12}$ is -$R_{13}$, -$OR_{13}$, or -$NR_{14}R_{15}$;

$R_{13}$ is

(a) hydrogen,

(b) -($C_1$-$C_5$) linear or branched alkyl optionally substituted with halogen, or

(c) phenyl optionally substituted with halogen;

$R_{14}$ and $R_{15}$ are independently selected from the group consisting of:

(a) hydrogen,

(b) -($C_1$-$C_5$) linear or branched alkyl optionally substituted with halogen, and

(c) phenyl optionally substituted with halogen;

n, m and p are independently an integer from 0 - 3;

y is an integer from 0 - 2; and

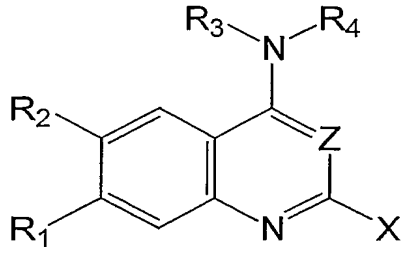
y + (m + p) equals an integer from 1 - 8;

or a purified stereoisomer or stereoisomer mixture of said compound or a salt of said compound or purified stereoisomer or stereoisomer mixture thereof.

Embodiment 2, more preferred compounds

The more preferred compounds of embodiment 2 have general formula (I) and are further defined below. In the following description of these more preferred compounds, the definitions for the various groups and variables represent the more preferred definitions when they differ from those of embodiment 2 as broadly defined above, and are to be understood as independent of each other.

The more preferred compounds of embodiment 2 have the formula (I)



(I)

wherein:

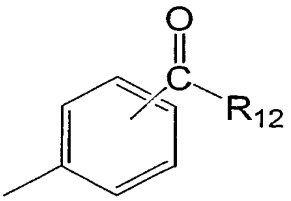
Z is N;

X is $NR_5R_6$;

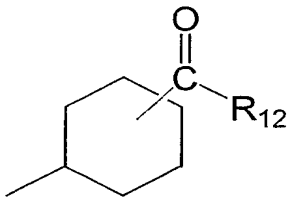
$R_1$ and $R_2$ are hydrogen;

$R_3$ is hydrogen;

$R_4$ is $-(CH_2)_yR_4'$, wherein



or



;

$R_4'$ is:

$R_5$ has the formula $-(CHR_{11})_m$-A or $-(CHR_{11})_p$-O-A, wherein $R_{11}$ is H and A is selected from the group consisting of:

(a) $-(C_1-C_5)$ linear or branched alkyl optionally substituted with $-(C_1-C_5)$ alkoxy,

(b) -phenyl optionally substituted with one to two substituents selected from the group consisting of:

(1) halogen,

(2) $-(C_1-C_5)$-alkoxy wherein the alkyl is optionally substituted with halogen,

(3) $-C(=O)OR_7$,

(4) $-C(=O)NR_8R_9$,

(5) morpholino,

and

(c) a saturated or fully unsaturated five or six membered heterocyclic ring containing one to two heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring contains at least one carbon atom, and is optionally substituted with oxo,

$R_6$ is hydrogen,

or

$R_5$ and $R_6$ form, together with the nitrogen to which they are attached, a saturated five or six membered heterocyclic ring, optionally containing one additional heteroatom selected from the group consisting of nitrogen and oxygen, wherein said heterocyclic ring is optionally substituted with $-(C_1-C_5)$-alkyl;

$R_7$ is selected from the group consisting of hydrogen, $-(C_1-C_5)$ linear or branched alkyl, and phenyl, which are optionally substituted with one halogen substituent,

$R_8$ and $R_9$ are independently selected from the group consisting of:

(a) hydrogen, and

(b) $-(C_1-C_5)$ linear or branched alkyl

(c) -phenyl, and

wherein (c) is optionally substituted with one substituent selected from the group consisting of halogen and $-(C_1-C_5)$ alkoxy ,

$R_{10}$ is $-NR_8R_9$ or $-OR_{11}$ ,

each occurrence of $R_{11}$ is hydrogen,

$R_{12}$ is $-OR_{13}$, or $-NR_{14}R_{15}$;

$R_{13}$ is

(a) hydrogen, or

(b) -($C_1$-$C_5$) linear or branched alkyl

(c) -($C_1$-$C_5$) linear or branched alkyl optionally substituted with halogen,

$R_{14}$ and $R_{15}$ are independently selected from the group consisting of:

(a) hydrogen,

(b) -($C_1$-$C_5$) linear or branched alkyl , and

(c) phenyl optionally substituted with halogen;

n, m and p are independently an integer from 0 - 3;

y is an integer from 0 - 2; and

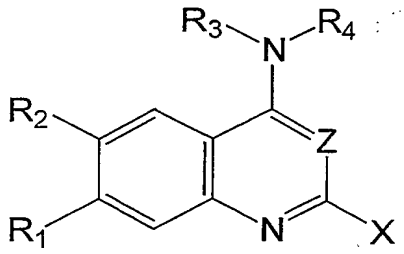
y + (m + p) equals an integer from 1 - 8;

or a purified stereoisomer or stereoisomer mixture of said compound or a salt of said compound or purified stereoisomer or stereoisomer mixture thereof.

Embodiment 3, preferred compounds

The preferred compounds of embodiment 3 have general formula (I) and are further defined below. In the following description of these preferred compounds, the definitions for the various groups and variables represent the preferred definitions when they differ from those of embodiment 3 as broadly defined above, and are to be understood as independent of each other.

The preferred compounds of embodiment 3 have the formula (I)




(I)

wherein:

Z is N;

X is $OR_5$ or $NR_5R_6$;

$R_1$ and $R_2$ are independently selected from the group consisting of hydrogen and $-OCH_3$ wherein at least one of $R_1$ and $R_2$ is $-OCH_3$;

$R_3$ is hydrogen;

$R_4$ is $-(CH_2)_y-R_4'$ wherein:

$R_4'$ is selected from the group consisting of:

(a) $-(C_1-C_5)$ linear or branched alkyl which is optionally substituted with one to three substituents selected from the group consisting of:

(1) $-C(=O)R_7$,

(2) $-C(=O)OR_7$,

(3) $-C(=O)NR_8R_9$,

(4) $-S(=O)R_{10}$, and

(5) $-S(=O)_2R_{10}$,

(b) $-(C_3-C_8)$ cycloalkyl,

(c) $-(C_6-C_{10})$ aryl,

wherein (b) and (c) are optionally substituted with one to three substituents selected from the group consisting of

(1) cyano,

(2) halogen,

(3) $-(CH_2)_nC(=O)R_7$,

(4) $-(CH_2)_nC(=O)OR_7$,

(5) $-(CH_2)_nC(=O)C(=O)-OR_7$

(6) $-(CH_2)_nC(=O)NR_8R_9$,

(7) $-S(=O)R_{10}$,

(8) $-S(=O)_2R_{10}$;

(9) $-C(=N-R_{10})-C_1-C_5$ alkyl, and

(10) a saturated or unsaturated four to six membered heterocyclic ring containing one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur wherein said ring contains at least one carbon atom,

and

(d) a saturated or fully unsaturated four to eight membered heterocyclic ring containing one to two heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring contains at least one carbon atom and wherein said ring is optionally substituted with one to three substituents selected from the group consisting of oxo, -($C_1$-$C_5$) alkoxy, -$(CH_2)_nC(=O)OR_7$, -$(CH_2)_nC(=O)NR_8R_9$, -$S(=O)R_{10}$, -$S(=O)_2R_{10}$ and –($C_1$-$C_5$) linear or branched alkyl optionally substituted by halogen;

or

$R_3$ and $R_4$ form, together with the nitrogen to which they are attached, a saturated four to eight membered heterocyclic ring, wherein the nitrogen is the only heteroatom, which is optionally substituted with one substituent selected from the group consisting of -$(CH_2)_nC(=O)OR_7$ and –($C_1$-$C_5$) linear or branched alkyl optionally substituted by halogen;

$R_5$ has the formula:

-$(CH_2)_p$-O-A where A is selected from the group consisting of:

(a) hydrogen,

(b) -($C_1$-$C_5$) linear or branched alkyl, optionally substituted with halogen, -($C_1$-$C_5$) alkoxy or -$NR_8R_9$,

(c) -($C_6$-$C_{10}$)-aryl, optionally substituted with one to three substituents selected from the group consisting of:

(1) halogen,

(2) -($C_1$-$C_5$)-alkyl optionally substituted with halogen,

(3) -($C_1$-$C_5$)-alkoxy,

(4) -$C(=O)OR_7$, and

(5) -$C(=O)NR_8R_9$,

or

-$(CH_2)_m$-A where A is selected from the group consisting of:

(a) -($C_1$-$C_5$) linear or branched alkyl optionally substituted with halogen, -($C_1$-$C_5$) alkoxy or -$NR_8R_9$,

(b) -($C_6$-$C_{10}$)-aryl, optionally substituted with one to three substituents selected from the group consisting of:

(1) halogen,

(2) -($C_1$-$C_5$)-alkoxy wherein the alkyl is optionally substituted with -$NR_8R_9$ or halogen,

(3) -$C(=O)R_7$,

(4) -$C(=O)OR_7$,

(5) -$C(=O)NR_8R_9$,

(6) -$S(=O)R_{10}$;

(7) -$S(=O)_2R_{10}$; and

(8) a saturated or fully unsaturated four to eight membered heterocyclic ring containing one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring:

(a8) contains at least one carbon atom;

(b8) is directly linked to the –($C_6$-$C_{10}$)-aryl or is linked to the –($C_6$-$C_{10}$)-aryl via an -O- linkage, and

(c8) is optionally substituted with –($C_1$-$C_5$)-alkyl, -$(CH_2)_nC(=O)OR_7$ or -$(CH_2)_nC(=O)NR_8R_9$,

(c) a saturated or fully unsaturated five to six membered heterocyclic ring containing one to two heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring contains at least one carbon atom, and is optionally substituted with oxo

and

(d) a fused bicyclo ring wherein one ring is a saturated or fully unsaturated five to six membered heterocyclic ring which contains one to three heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said heterocyclic ring contains at least one

carbon atom and the other ring is a saturated five to six membered carbocycle;

$R_6$ is selected from the group consisting of:

(a) hydrogen, and

(b) -($C_1$-$C_5$) linear or branched alkyl,

or

$R_5$ and $R_6$ form, together with the nitrogen to which they are attached, a saturated five to seven membered heterocyclic ring, which optionally contains one additional heteroatom selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring is optionally substituted with one to three substituents selected from the group consisting of:

(a) halogen,

(b) oxo,

(c) -($C_1$-$C_5$) linear or branched alkyl optionally substituted by halogen or –($C_1$-$C_5$) alkoxy,

(d) -$(CH_2)_n COOR_7$,

(e) -$(CH_2)_n CONR_8R_9$,

(f) -$(CH_2)_n$-Q, wherein Q is pyridyl,

wherein,

(i) $R_3 \neq R_4$,

(ii) $R_5 \neq R_6$, and

(iii) ($R_3$ and $R_4$) ≠ ($R_5$ and $R_6$)

$R_7$ is selected from the group consisting of hydrogen, -($C_1$-$C_5$) linear or branched alkyl and phenyl, which are optionally substituted with one to three substituents selected from the group consisting of halogen, oxo, -($C_1$-$C_5$) alkoxy , and –($C_1$-$C_5$) linear or branched alkyl optionally substituted by halogen;

$R_8$ and $R_9$ are independently selected from the group consisting of hydrogen, -($C_1$-$C_5$) linear or branched alkyl, and –($C_6$-$C_{10}$) aryl which is optionally substituted with one to three substituents selected from the group consisting of halogen and -($C_1$-$C_5$) alkoxy, or

$R_8$ and $R_9$ form, together with the nitrogen to which they are attached, a saturated or fully unsaturated, five or six membered heterocyclic ring, wherein said ring has one to two additional heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur,

$R_{10}$ is hydrogen, -$NR_8R_9$, -$OR_{11}$, -($C_1$-$C_5$) linear or branched alkyl, or phenyl;

$R_{11}$ is hydrogen, -($C_1$-$C_5$) linear or branched alkyl, or phenyl;

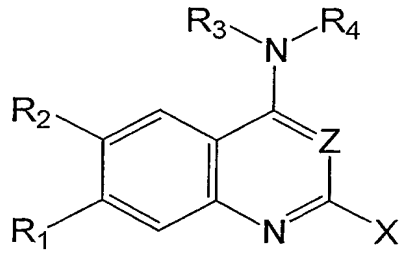
n, m and p are independently an integer from 0 - 3; and

y is an integer from 0 - 2,

or a purified stereoisomer or stereoisomer mixture of said compound or a salt of said compound or purified stereoisomer or stereoisomer mixture thereof.

The more preferred compounds of embodiment 3 have general formula (I) and are further defined below. In the following description of these more preferred compounds, the definitions for the various groups and variables represent the more preferred definitions when they differ from those of embodiment 3 as broadly defined above, and are to be understood as independent of each other.

The more preferred compounds of embodiment 3 have the formula (I)



(I)

wherein,

Z is N;

X is $NR_5R_6$;

$R_1$ and $R_2$ are independently selected from the group consisting of hydrogen and $-OCH_3$ wherein at least one of $R_1$ and $R_2$ is $-OCH_3$;

$R_3$ is hydrogen;

$R_4$ is $-(CH_2)_y-R_4'$ wherein:

$R_4'$ is selected from the group consisting of:

(a) -cyclohexyl,

(b) -phenyl,

wherein (a) and (b) are optionally substituted with one to three substituents selected from the group consisting of

(1) $-(CH_2)_nC(=O)R_7$,

(2) $-(CH_2)_nC(=O)OR_7$,

(3) $-(CH_2)_nC(=O)NR_8R_9$,

(4) $-S(=O)R_{10}$,

(5) $-S(=O)_2R_{10}$;

(6) $-C(=N-R_{10})-C_1-C_5$ alkyl, and

(7) a saturated or fully unsaturated six membered heterocyclic ring containing one to two heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur,

and

(c) a fully unsaturated five membered heterocyclic ring containing one sulfur or oxygen, wherein said ring is optionally substituted with one substituent selected from the group consisting of $-(CH_2)_nC(=O)OR_7$, $-(CH_2)_nC(=O)NR_8R_9$, $-S(=O)R_{10}$, and $-S(=O)_2R_{10}$;

or

$R_3$ and $R_4$ form, together with the nitrogen to which they are attached, a saturated six membered heterocyclic ring, wherein the nitrogen is the only heteroatom, which is unsubstituted;

$R_5$ has the formula:

$-(CH_2)_p-O-A$ where A is selected from the group consisting of:

(a) $-(C_1-C_5)$ linear or branched alkyl, optionally substituted with halogen, and

(b) -phenyl, optionally substituted with one to three substituents selected from the group consisting of:

(1) halogen, and

(2) $-(C_1-C_5)$-alkoxy,

or

$-(CH_2)_m-A$ where A is selected from the group consisting of:

(a) $-(C_1-C_5)$ linear or branched alkyl optionally substituted with $-(C_1-C_5)$ alkoxy,

(b) -phenyl, substituted with one to two substituents selected from the group consisting of:

(1) halogen,

(2) $-(C_1-C_5)$-alkoxy wherein the alkyl is optionally substituted with halogen,

(3) $-C(=O)OR_7$,

(4) $-C(=O)NR_8R_9$, and

(5) -morpholinyl,

(c) a saturated or fully unsaturated five or six membered heterocyclic ring containing one to two heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, optionally substituted with oxo,

and

(f) a fused bicyclo ring wherein one ring is a saturated or fully unsaturated five to six membered heterocyclic ring which contains one

heteroatom selected from the group consisting of nitrogen and oxygen, wherein said heterocyclic ring contains at least one carbon atom and the other ring is a saturated six membered carbocycle;

$R_6$ is hydrogen,

or

$R_5$ and $R_6$ form, together with the nitrogen to which they are attached, a saturated five or six membered heterocyclic ring, which optionally contains one additional heteroatom selected from the group consisting of nitrogen, oxygen and sulfur wherein said ring is optionally substituted with one or two substituents selected from the group consisting of:

(a) -($C_1$-$C_5$) linear or branched alkyl optionally substituted by halogen or –($C_1$-$C_5$) alkoxy,

(b) -$(CH_2)_nCOOR_7$, and

(c) -$(CH_2)_nCONR_8R_9$,

wherein,

(i) $R_3 \neq R_4$,

(ii) $R_5 \neq R_6$, and

(iii) ($R_3$ and $R_4$) ≠ ($R_5$ and $R_6$)

$R_7$ is selected from the group consisting of hydrogen, -($C_1$-$C_5$) linear or branched alkyl and phenyl, which are optionally substituted with one to three halogen substituents;

$R_8$ and $R_9$ are independently selected from the group consisting of hydrogen, -($C_1$-$C_5$) linear or branched alkyl, and phenyl which is optionally substituted with one substituent selected from the group consisting of halogen and -($C_1$-$C_5$) alkoxy,

$R_{10}$ is -$NR_8R_9$ or -$OR_{11}$,

$R_{11}$ is hydrogen, or -($C_1$-$C_5$) linear or branched alkyl

n, m and p are independently an integer from 0 - 3; and

y is an integer from 0 - 2,

or a purified stereoisomer or stereoisomer mixture of said compound or a salt of said compound or purified stereoisomer or stereoisomer mixture thereof.

Pharmaceutically acceptable salts of these preferred and more preferred compounds as well as commonly used prodrugs of these compounds are also within the scope of the invention.

Salts are especially the pharmaceutically acceptable salts of compounds of formulae (I) or (II) such as, for example, organic or inorganic acid addition salts of compounds of formulae (I) or (II). Suitable inorganic acids include but are not limited to halogen acids (such as hydrochloric acid), sulfuric acid, or phosphoric acid. Suitable organic acids include but are not limited to carboxylic, phosphonic, sulfonic, or sulfamic acids, with examples including acetic acid, trifluoroacetic acid, propionic acid, octanoic acid, decanoic acid, dodecanoic acid, glycolic acid, lactic acid, 2- or 3-hydroxybutyric acid, γ-aminobutyric acid (GABA), gluconic acid, glucosemonocarboxylic acid, benzoic acid, salicylic acid, phenylacetic acid, mandelic acid, methanesulfonic acid, trifluoromethanesulfonic acid, fumaric acid, oxalic acid, succinic acid, adipic acid, pimelic acid, suberic acid, azeiaic acid, malic acid, tartaric acid, citric acid, glucaric acid, galactaric acid, amino acids (such as glutamic acid, aspartic acid, N-methylglycine, acetytaminoacetic acid, N-acetylasparagine or N-acetylcysteine), pyruvic acid, acetoacetic acid, phosphoserine, and 2- or 3-glycerophosphoric acid.

In addition, pharmaceutically acceptable salts include acid salts of inorganic bases, such as salts containing alkaline cations (e.g., $Li^+$ $Na^+$ or $K^+$), alkaline earth cations (e.g., $Mg^{+2}$, $Ca^{+2}$ or $Ba^{+2}$), the ammonium cation, as well as acid salts of organic bases, including aliphatic and aromatic substituted ammonium, and quaternary ammonium cations such as those arising from protonation or peralkylation of triethylamine, *N,N*-diethylamine, *N,N*-dicyclohexylamine, pyridine, *N,N*-dimethylaminopyridine (DMAP), 1,4-

diazabicyclo[2.2.2]octane (DABCO), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

Prodrugs are considered to be any covalently bonded carriers which release the active parent compound of formula (I) or (II) *in vivo*. Formation of prodrugs is well known in the art in order to enhance the properties of the parent compound; such properties include solubility, absorption, biostability and release time (see *"Pharmaceutical Dosage Form and Drug Delivery Systems"* (Sixth Edition), edited by Ansel et al., publ. by Williams & Wilkins, pgs. 27-29, (1995) which is hereby incorporated by reference).

Commonly used prodrugs of the disclosed compounds of formula (I) and (II) are designed to take advantage of the major drug biotransformation reactions and are also to be considered within the scope of the invention. Major drug biotransformation reactions include N-dealkylation, O-dealkylation, aliphatic hydroxylation, aromatic hydroxylation, N-oxidation, S-oxidation, deamination, hydrolysis reactions, glucuronidation, sulfation and acetylation (see *Goodman and Gilman's The Pharmacological Basis of Therapeutics* (Tenth Edition), editor Hardman et al., publ. by McGraw-Hill, pages 12-18, (2001), which is hereby incorporated by reference).

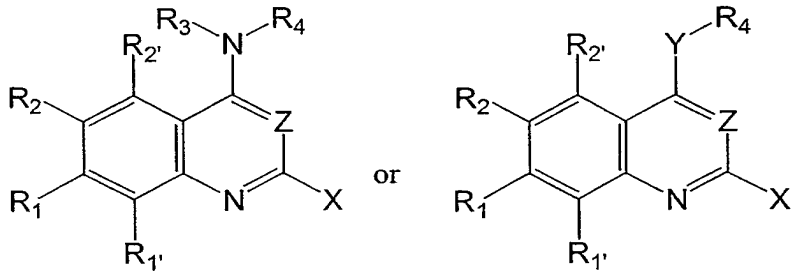
*Definitions*

The term "halogen" as it appears in the specification and claims refers to fluorine, chlorine, bromine, and iodine substituents for the purposes of this invention. When halogen is a possible substituent on an alkyl group, the alkyl may be fully substituted, up to perhalo.

The term "fused bicyclo ring" as it appears in the specification and claims refers to a substituent which is a two ring structure which share two carbon atoms. The bonding between the fused bicyclo ring and the compound and/or atom to which it is attached can be through either of the two rings.

***Description of the Compositions***

The compounds described by formulas (I) and (II) above, or the purified stereoisomer or stereoisomer mixture of said compound or a salt of said compound or purified stereoisomer or stereoisomer mixture thereof, are useful as prolylpeptidase inhibitors, inducers of apoptosis and cancer treatment agents. However, the full scope of compounds which are contemplated for use as prolylpeptidase inhibitors, inducers of apoptosis and cancer treatment agents are described by the compounds of formula (Ia) and (IIa):



(Ia) or (IIa)

wherein,

Z is CH or N;

Y is O or S;

X is $OR_5$ or $NR_5R_6$;

$R_1$, $R_{1'}$, $R_2$ and $R_{2'}$ are independently selected from the group consisting of hydrogen, amino, cyano, halogen, hydroxy, methoxy and nitro;

$R_3$ is selected from the group consisting of:

(a) hydrogen, and

(b) -($C_1$-$C_{10}$) linear or branched alkyl,

$R_4$ is -$(CH_2)_y$-$R_4$' wherein:

$R_4$' is selected from the group consisting of:

(a) -($C_1$-$C_5$) linear or branched alkyl which is optionally substituted with one to three substituents selected from the group consisting of:

(1) cyano,

(2) halogen,

(3) hydroxy,

(4) nitro,

(5) -($C_1$-$C_5$) linear or branched alkyl optionally substituted by halogen,

(6) -($C_1$-$C_5$) alkoxy,

(7) -C(=O)$R_7$,

(8) -C(=O)O$R_7$,

(9) -C(=O)N$R_8R_9$,

(10) -S(=O)$R_{10}$, and

(11) -S(=O)$_2R_{10}$;

(b) -$C_3$-$C_8$ cycloalkyl,

(c) -$C_6$-$C_{10}$ aryl,

wherein (b) and (c) are optionally substituted with one to three substituents selected from the group consisting of

(1) amino,

(2) cyano,

(3) halogen,

(4) hydroxy,

(5) nitro,

(6) oxo,

(7) -($C_1$-$C_5$) linear or branched alkyl optionally substituted by halogen or hydroxy,

(8) -($C_1$-$C_5$) haloalkoxy,

(9) -$(CH_2)_n$C(=O)$R_7$,

(10) -$(CH_2)_n$C(=O)O$R_7$,

(11) -$(CH_2)_n$C(=O)C(=O)-O$R_7$,

(12) -$(CH_2)_n$C(=O)N$R_8R_9$,

(13) -S(=O)$R_{10}$,

(14) -S(=O)$_2R_{10}$,

(15) -C(=N-$R_{10}$)-$C_1$-$C_5$-alkyl, and

(16) a saturated or unsaturated four to six membered heterocyclic ring containing one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring contains at least one carbon atom,

and

(d) a saturated or unsaturated four to six membered heterocyclic ring containing one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring contains at least one carbon atom and wherein said ring is optionally substituted with one to three substituents selected from the group consisting of amino, cyano, halogen, hydroxy, nitro, oxo, -($C_1$-$C_5$) -alkoxy, -$(CH_2)_nC(=O)OR_7$, -$(CH_2)_nC(=O)NR_8R_9$, -$S(=O)R_{10}$, -$S(=O)_2R_{10}$ and -($C_1$-$C_5$) linear or branched alkyl optionally substituted by halogen;

or

$R_3$ and $R_4$ form, together with the nitrogen to which they are attached, a saturated or unsaturated, four to eight membered heterocyclic ring, wherein the nitrogen is the only heteroatom, which is optionally substituted with one to three substituents selected from the group consisting of amino, cyano, halogen, hydroxy, nitro, oxo, -($C_1$-$C_5$) alkoxy, phenyl, -$C(=O)R_7$, -$(CH_2)_nC(=O)OR_7$, -$(CH_2)_nC(=O)NR_8R_9$, -$S(=O)R_{10}$, -$S(=O)_2R_{10}$ and -($C_1$-$C_5$) linear or branched alkyl optionally substituted by halogen;

$R_5$ has the formula $(CHR_{11})_m$-A or $(CHR_{11})_p$-O-A, where A is selected from the group consisting of:

(a) hydrogen,

(b) -($C_1$-$C_5$) linear or branched alkyl optionally substituted with cyano, halogen, hydroxy, -($C_1$-$C_5$) alkoxy or -$NR_8R_9$,

(c) -$C_3$-$C_8$ cycloalkyl optionally substituted with cyano, halogen, hydroxy, -($C_1$-$C_5$)-alkyl, -($C_1$-$C_5$) alkoxy or -$NR_8R_9$,

(d) -$C_6$-$C_{10}$ aryl optionally substituted with one to three substituents selected from the group consisting of:

(1) cyano,

(2) halogen,

(3) hydroxy,

(4) nitro,

(5) -$NR_8R_9$,

(6) -($C_1$-$C_5$) linear or branched alkyl optionally substituted with -$NR_8R_9$ or halogen,

(7) -($C_1$-$C_5$) alkoxy wherein the alkyl is optionally substituted with -$NR_8R_9$ or halogen,

(8) $C_6$-$C_{10}$-aryl-($C_1$-$C_5$)-alkoxy-

(9) $C_6$-$C_{10}$-aryloxy- optionally substituted with halogen,

(10) -$C_6$-$C_{10}$-aryl optionally substituted with halogen,

(11) -$CH_2$-$C_6$-$C_{10}$-aryl,

(12) -C(=O)$R_7$,

(13) -C(=O)$OR_7$,

(14) -C(=O)$NR_8R_9$,

(15) -S(=O)$R_{10}$,

(16) -$S(=O)_2R_{10}$, and

(17) a saturated or unsaturated four to eight membered heterocyclic ring containing one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring:

(a17) contains at least one carbon atom;

(b17) is directly linked to the -$C_6$-$C_{10}$-aryl or is linked to the -$C_6$-$C_{10}$-aryl via an -O- linkage; and

(c17) is optionally substituted with -($C_1$-$C_5$)-alkyl, -$(CH_2)_n$C(=O)$OR_7$ or -$(CH_2)_n$C(=O)$NR_8R_9$,

(e) a saturated or unsaturated four to eight membered heterocyclic ring containing one to four heteroatoms selected from the group consisting

of nitrogen, oxygen and sulfur, wherein said ring contains at least one carbon atom, and is optionally substituted with

(1) -($C_1$-$C_5$)-alkyl optionally substituted by halogen,

(2) phenyl optionally substituted by halogen,

(3) -($C_1$-$C_5$)-alkoxy- wherein the alkyl is optionally substituted with halogen,

(4) $C_6$-$C_{10}$-aryloxy- wherein the aryl is optionally substituted with halogen, or

(5) oxo;

(f) a fused bicyclo ring wherein one ring is a saturated or unsaturated five to six membered saturated or unsaturated heterocyclic ring which contains one to three heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said heterocyclic ring contains at least one carbon atom, and the other ring is a saturated or unsaturated five to eight membered carbocyclic ring,

and

(g) a fused bicyclo ring wherein each ring is independently a saturated or unsaturated five to eight membered carbocyclic ring;

$R_6$ is selected from the group consisting of:

(a) hydrogen, and

(b) -($C_1$-$C_5$) linear or branched alkyl;

wherein $R_5$ and $R_6$ are not both hydrogen;

or

$R_5$ and $R_6$ form, together with the nitrogen to which they are attached, a saturated or unsaturated four to eight membered heterocyclic ring, which optionally contains one to three additional nitrogen atoms wherein said ring contains at least one carbon

atom, and wherein said ring is optionally substituted with one to three substituents selected from the group consisting of:

(a) amino,

(b) cyano,

(c) halogen,

(d) hydroxy,

(e) nitro,

(f) oxo,

(g) --($C_1$-$C_5$) linear or branched alkyl optionally substituted by halogen or -($C_1$-$C_5$) alkoxy,

(h) -($C_1$-$C_5$) alkoxy,

(i) -($C_1$-$C_5$)-alkoxy-($C_1$-$C_5$) alkyl,

(j) -$C_6$-$C_{10}$-aryl optionally substituted by halogen or -($C_1$-$C_5$) alkyl,

(k) -($C_1$-$C_5$)-alkyl-phenyl optionally substituted by halogen or -($C_1$-$C_5$)-alkyl,

(l) -$(CH_2)_nCOOR_7$,

(m) -$(CH_2)_nCONR_8R_9$,

(n) -$(CH_2)_nNR_8R_9$,

(o) -$S(=O)R_{10}$,

(p) -$S(=O)_2R_{10}$, and

(q) -$(CH_2)_n$-Q, wherein Q:

(q1) a four to eight membered saturated or unsaturated heterocyclic ring containing one to four nitrogens, wherein said ring contains at least one carbon atom, or

(q2) -$C_6$-$C_{10}$-aryl optionally substituted with halogen or -($C_1$-$C_5$)-alkyl;

$R_7$ is selected from the group consisting of hydrogen, -($C_1$-$C_5$) linear or branched alkyl, phenyl, -($C_1$-$C_5$)-alkyl-phenyl, and -$C_3$-$C_{10}$ cycloalkyl which are optionally substituted with one to three substituents selected from the group consisting of halogen, oxo, -($C_1$-$C_5$) alkoxy, -$C(=O)R_7$ -$(CH_2)_nC(=O)OR_7$, -$(CH_2)_nC(=O)NR_8R_9$, -$S(=O)R_{10}$, -$S(=O)_2R_{10}$ and -($C_1$-$C_5$) linear or branched alkyl optionally substituted by halogen;

$R_8$ and $R_9$ are independently selected from the group consisting of:

(a) hydrogen,

(b) -($C_1$-$C_5$) linear or branched alkyl which is optionally substituted with a substituent selected from the group consisting of halogen and -($C_1$-$C_5$) alkoxy,

(c) -($C_1$-$C_5$) alkoxy-,

(d) -$C_6$-$C_{10}$ aryl, and

(e) -$(CH_2)_n$-R wherein R is a saturated or unsaturated five to six membered heterocyclic ring containing one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring contains at least one carbon atom,

wherein (c)-(e) are optionally substituted with one to three substituents selected from the group consisting of halogen, -($C_1$-$C_5$) alkylamino, -($C_1$-$C_5$) alkoxy, -C(=O)$R_7$, -$(CH_2)_n$C(=O)$OR_7$, -$(CH_2)_n$C(=O)$NR_8R_9$, -S(=O)$R_{10}$, -$S(=O)_2R_{10}$ and -($C_1$-$C_5$) linear or branched alkyl optionally substituted by halogen,

or

$R_8$ and $R_9$ form, together with the nitrogen to which they are attached, a saturated or unsaturated four to eight membered heterocyclic ring, optionally containing one to three additional heteroatoms selected from the group consisting of nitrogen and oxygen, wherein said ring contains at least one carbon atom and wherein said heterocyclic ring is optionally substituted with -($C_1$-$C_5$) linear or branched alkyl;

$R_{10}$ is hydrogen, -$NR_8R_9$, -$OR_{11}$, -($C_1$-$C_5$) linear or branched alkyl, or phenyl;

each occurrence of $R_{11}$ is independently selected from the group consisting of hydrogen, -$C_1$-$C_5$ linear or branched alkyl and phenyl;

n, m and p are independently an integer from 0 - 3;

y is an integer from 0 - 2;

or a purified stereoisomer or stereoisomer mixture of said compound or a salt of said compound or purified stereoisomer or stereoisomer mixture thereof.

The compounds of formula (I) and (II) as described above are believed to be novel compounds. The scope of the compounds described by formula (Ia) and (IIa) encompass the compounds defined by formula (I) and (II) as well as compounds described in the prior art references cited below:

Lacefield et al. (U.S. Patent No. 3,956,495) describes 2,4-diaminoquinazoline compounds which are used as antithrombotic agents.

Ife et al. (U.S. Patent No. 5,064,833) described substituted quinazoline compounds which are used in the treatment of diseases of the stomach based on excessive gastric acid secretion.

Pfizer, Inc. (GB 1,156,973) describes 2,4-diaminoquinazoline compounds which are used to reduce blood pressure in hypertensive subjects.

Coe et al. (WO 92/07844 and WO 92/14716) describes 2,4-diaminoquinazoline compounds which are used to potentiate chemotherapeutic agents in the treatment of cancer.

Sayed et al. (*Pakistan. J. Sci. Ind. Res.*, vol. 28, no. 6, pages 367-371, Dec. 1985) 6-bromo-2,4-diaminoquinazoline compounds. No data was provided on the activity of these compounds.

Stankovský et al. (*Coll. Czech. Chem. Commun.*, vol. 45, pages 1079-1085, (1980) and *Chem. Zvesti*, vol. 37(6): 831-836, (1983)) describe synthetic procedures to form 4-anilinoquinazoline compounds. No data was provided on the activity of these compounds.

Singhal et al. (*J. Indian Chem Soc.*, vol. LXI, pages 690-693, August 1984) describe 2,4-diaminoquinazoline compounds and their use as antimalarial agents.

Abou-Zeid et al. (*Egypt. J. Pharm. Sci.*, vol. 32, no. 1-2, pages 165-174, (1991)) described 1,4-disubstituted piperazines (which happen to also be 2,4-diaminoquinazoline compounds) and their use as antihypertensive agents.

In each case, the above prior art reference did not recognize the use of their compounds as being inhibitors of prolylpeptidase, inducers of apoptosis or useful in the treatment of cancer.

The invention also includes pharmaceutical compositions comprising a therapeutically effective amount of one or more of the compounds or purified stereoisomers or stereoisomer mixtures of the invention, or their salts or prodrugs forms thereof, with a pharmaceutically acceptable ingredient.

The pharmaceutical compositions are prepared so that they may be administered orally, dermally, parenterally, nasally, ophthalmically, otically, sublingually, rectally or vaginally. Dermal administration includes topical application or transdermal administration. Parenteral administration includes intravenous, intraarticular, intramuscular, and subcutaneous injections, as well as use of infusion techniques. One or more compounds of the invention may be present in association with one or more non-toxic pharmaceutically acceptable ingredients and optionally, other active anti-proliferative agents, to form the pharmaceutical composition. These compositions can be prepared by applying known techniques in the art such as those taught in *Remington's Pharmaceutical Sciences* (Fourteenth Edition), Managing Editor, John E. Hoover, Mack Publishing Co., (1970) or *Pharmaceutical Dosage Form and Drug Delivery Systems* (Sixth Edition), edited by Ansel et al., publ. by Williams & Wilkins, (1995), each of which is hereby incorporated by reference.

Commonly used pharmaceutical ingredients which can be used as appropriate to formulate the composition for its intended route of administration include:

**acidifying agents** (examples include but are not limited to acetic acid, citric acid, fumaric acid, hydrochloric acid, nitric acid);

**alkalinizing agents** (examples include but are not limited to ammonia solution, ammonium carbonate, diethanolamine, monoethanolamine, potassium hydroxide, sodium borate, sodium carbonate, sodium hydroxide, triethanolamine, trolamine);

**adsorbents** (examples include but are not limited to powdered cellulose and activated charcoal);

**aerosol propellants** (examples include but are not limited to carbon dioxide, $CCl_2F_2$, $F_2ClC$-$CClF_2$ and $CClF_3$)

**air displacement agents** (examples include but are not limited to nitrogen and argon);

**antifungal preservatives** (examples include but are not limited to benzoic acid, butylparaben, ethylparaben, methylparaben, propylparaben, sodium benzoate);

**antimicrobial preservatives** (examples include but are not limited to benzalkonium chloride, benzethonium chloride, benzyl alcohol, cetylpyridinium chloride, chlorobutanol, phenol, phenylethyl alcohol, phenylmercuric nitrate and thimerosal);

**antioxidants** (examples include but are not limited to ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, hypophosphorus acid, monothioglycerol, propyl gallate, sodium ascorbate, sodium bisulfite, sodium formaldehyde sulfoxylate, sodium metabisulfite);

**binding materials** (examples include but are not limited to block polymers, natural and synthetic rubber, polyacrylates, polyurethanes, silicones and styrene-butadiene copolymers);

**buffering agents** (examples include but are not limited to potassium metaphosphate, potassium phosphate monobasic, sodium acetate, sodium citrate anhydrous and sodium citrate dihydrate)

**carrying agents** (examples include but are not limited to acacia syrup, aromatic syrup, aromatic elixir, cherry syrup, cocoa syrup, orange syrup, syrup, corn oil, mineral oil, peanut oil, sesame oil, bacteriostatic sodium chloride injection and bacteriostatic water for injection)

**chelating agents** (examples include but are not limited to edetate disodium and edetic acid)

**colorants** (examples include but are not limited to FD&C Red No. 3, FD&C Red No. 20, FD&C Yellow No. 6, FD&C Blue No. 2, D&C Green No. 5, D&C Orange No. 5, D&C Red No. 8, caramel and ferric oxide red);

**clarifying agents** (examples include but are not limited to bentonite);

**emulsifying agents** (examples include but are not limited to acacia, cetomacrogol, cetyl alcohol, glyceryl monostearate, lecithin, sorbitan monooleate, polyethylene 50 stearate);

**encapsulating agents** (examples include but are not limited to gelatin and cellulose acetate phthalate)

**flavorants** (examples include but are not limited to anise oil, cinnamon oil, cocoa, menthol, orange oil, peppermint oil and vanillin);

**humectants** (examples include but are not limited to glycerin, propylene glycol and sorbitol);

**levigating agents** (examples include but are not limited to mineral oil and glycerin);

**oils** (examples include but are not limited to arachis oil, mineral oil, olive oil, peanut oil, sesame oil and vegetable oil);

**ointment bases** (examples include but are not limited to lanolin, hydrophilic ointment, polyethylene glycol ointment, petrolatum, hydrophilic petrolatum, white ointment, yellow ointment, and rose water ointment);

**penetration enhancers (transdermal delivery)** (examples include but are not limited to monohydroxy or polyhydroxy alcohols, saturated or unsaturated fatty alcohols, saturated or unsaturated fatty esters, saturated or unsaturated dicarboxylic acids, essential oils, phosphatidyl derivatives, cephalin, terpenes, amides, ethers, ketones and ureas)

**plasticizers** (examples include but are not limited to diethyl phthalate and glycerin);

**solvents** (examples include but are not limited to alcohol, corn oil, cottonseed oil, glycerin, isopropyl alcohol, mineral oil, oleic acid, peanut oil, purified water, water for injection, sterile water for injection and sterile water for irrigation);

**stiffening agents** (examples include but are not limited to cetyl alcohol, cetyl esters wax, microcrystalline wax, paraffin, stearyl alcohol, white wax and yellow wax);

**suppository bases** (examples include but are not limited to cocoa butter and polyethylene glycols (mixtures));

**surfactants** (examples include but are not limited to benzalkonium chloride, nonoxynol 10, oxtoxynol 9, polysorbate 80, sodium lauryl sulfate and sorbitan monopalmitate);

**suspending agents** (examples include but are not limited to agar, bentonite, carbomers, carboxymethylcellulose sodium, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, kaolin, methylcellulose, tragacanth and veegum);

**sweetening agents** (examples include but are not limited to aspartame, dextrose, glycerin, mannitol, propylene glycol, saccharin sodium, sorbitol and sucrose);

**tablet anti-adherents** (examples include but are not limited to magnesium stearate and talc);

**tablet binders** (examples include but are not limited to acacia, alginic acid, carboxymethylcellulose sodium, compressible sugar, ethylcellulose, gelatin, liquid glucose, methylcellulose, povidone and pregelatinized starch);

**tablet and capsule diluents** (examples include but are not limited to dibasic calcium phosphate, kaolin, lactose, mannitol, microcrystalline cellulose, powedered cellulose, precipitated calcium carbonate, sodium carbonate, sodium phosphate, sorbitol and starch);

**tablet coating agents** (examples include but are not limited to liquid glucose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose, ethylcellulose, cellulose acetate phthalate and shellac);

**tablet direct compression excipients** (examples include but are not limited to dibasic calcium phosphate);

**tablet disintegrants** (examples include but are not limited to alginic acid, carboxymethylcellulose calcium, microcrystalline cellulose, polacrillin potassium, sodium alginate, sodium starch glycollate and starch);

**tablet glidants** (examples include but are not limited to colloidal silica, corn starch and talc);

**tablet lubricants** (examples include but are not limited to calcium stearate, magnesium stearate, mineral oil, stearic acid and zinc stearate);

**tablet/capsule opaquants** (examples include but are not limited to titanium dioxide);

**tablet polishing agents** (examples include but are not limited to carnuba wax and white wax);

**thickening agents** (examples include but are not limited to beewax, cetyl alcohol and paraffin);

**tonicity agents** (examples include but are not limited to dextrose and sodium chloride);

**viscosity increasing agents** (examples include but are not limited to alginic acid, bentonite, carbomers, carboxymethylcellulose sodium, methylcellulose, povidone, sodium alginate and tragacanth); and

**wetting agents** (examples include but are not limited to heptadecaethylene oxycetanol, lecithins, polyethylene sorbitol monooleate, polyoxyethylene sorbitol monooleate, polyoxyethylene stearate,).

Depending on the route of administration, the compositions can take the form of aerosols, capsules, creams, elixirs, emulsions, foams, gels, granules, inhalants, lotions, magmas, ointments, peroral solids, powders, sprays, syrups, suppositories, suspensions, tablets and tinctures.

The compositions of the invention can also have an additional apoptosis inducers as an active ingredient. Examples of known apoptosis inducers (see e.g. Calbiochem's 2001 Signal Transduction Catalog, pages 702-704, the contents of which are incorporated by reference) which can be added to the described invention include but are not limited to A23187, N-Acetyl-L-cysteine, actinomycin D, tyrphostin A9, tyrphostin A25, AG 490, AG 1714, anandamide, anisomycin, aphidicolin, bafilomycin A1, berberine hemisulfate, betulinic acid, bleomycin sulfate, CAFdA, calphostin C, camptothecin, CAPE, chelerythrine chloride, 2-chloro-2'-deoxyadenosine, 2-chloro-2'-deoxyadenosine 5'-triphosphate, colcemid, cochicine, corticosterone, cycloheximide, cyclophosphamide monohydrate, cyclosporine A, daunorubicin hydrocloride, dexamethasone, 3,3'-diindolylmethane, dolastatin 15, doxorubicin hydrochloride, erbstatin analog, ET-18-$OCH_3$, etoposide, etoposide phosphate, 5-fluorouracil, folimycin, forskolin, genistein, glycodeoxycholic acid sodium salt, H-7 dihydrochloride, H-89 dihydrochloride, harringtonine, homoharringtonine, 4-hydroxynonenal, 4-hydroxyphenylretinamide, hydroxyurea, indanocine, ionomycin free acid, ionomycin calcium salt, KN-93, methotrexate, mitomycin C, okadaic acid, oligomycin, p53 activator, paclitaxel, phorbol-12-myristate-13-acetate, (pivaloyloxy)methyl butyrate, puromycin dihydrochloride, 1-pyrrolidinecarbodithioic acid ammonium salt, quercetin dihydrate, rapamycin, SNAP, SNOG, sodium butyrate, sodium 4-phenylbutyrate, spermine tetrachloride, D-*erythro*-sphingosine (free base; N-Acetyl-; N,N-dimethyl-; N-hexanoyl-; and N-octanoyl forms), staurosporine, sulfasalizine, sulindac, tamoxifen citrate, 4-hydroxy-(Z)-tamoxifen, thapsigargin, α-toxin, TRAIL, valinomycin, (±)-verapamil hydrochloride, veratridine and vitamin E succinate.

Additional known apoptosis inducers (see Oncogene catalog, the contents of which are incorporated by reference) include:

2β, 3β, 5β, 11α, 14α, 20R, 22R-Heptahydroxycholest-7-en-6-one, dactinomycin, DHAD; 1,4-dihydroxy-5,8-*bis*({2-[(2-hydroxyethyl)amino])-9,10-anthraquinone, 2HCl; N,N-hexamethylenebisacetamide (HMBA); mitoxanthrone, dihydrochloride; MurA; Muristerone A; NSC-301739; SAHA; suberoylanilide, hydroxamic acid; caspase-3 (Ab-4) Monoclonal Antibody; active caspase-7 (Ab-1) Polyclonal Antibody; caspase-12 (Ab-1) Polyclonal Antibody; caspase-12 (Ab-2) Polyclonal Antibody; caspase-13 (Ab-1) Polyclonal Antibody; acinus (Ab-1) Polyclonal Antibody; acinus (Ab-2) Polyclonal Antibody; acinus (Ab-3) Polyclonal Antibody; acinus (Ab-4) Polyclonal Antibody; AIF (Ab-1) Polyclonal Antibody;

AIF (Ab-2) Polyclonal Antibody; Phospho-Bad (Ab-1) Polyclonal Antibody; Phospho-Bad (Ab-2) Polyclonal Antibody; Bid (Ab-1) Polyclonal Antibody; Bid (Ab-2) Polyclonal Antiserum; Bid (Ab-3) Polyclonal Antiserum; Bnip3L (Ab-1) Polyclonal Antibody; DRAK1 (Ab-1) Polyclonal Antibody; DRAK2 (Ab-1) Polyclonal Antibody; Fas (Ab-6) Polyclonal Antibody; FLASH (Ab-1) Polyclonal Antiserum; p110 Mitochondrial Protein (Ab-1) Monoclonal Antibody; pTEN (Ab-4) Polyclonal Antibody; Rb Associated Protein 46 (Ab-1) Polyclonal Antibody; Rb Associated Protein 48 (Ab-1) Polyclonal Antibody; RIP (Ab-1) Polyclonal Antibody; RIP2 (Ab-1) Polyclonal Antibody; Smac/DIABLO (Ab-3) Polyclonal Antibody; TWEAK (Ab-1) Polyclonal Antibody; VDAC (Ab-1) Polyclonal Antibody; Bad Control Proteins; and Fas Ligand Plus™ Recombinant Human Protein.

Optional cancer treatment agents which can be added to the composition include but are not limited to compounds listed on the cancer chemotherapy drug regimens in the 11$^{th}$ Edition of the Merck Index, (1996), which is hereby incorporated by reference, such as asparaginase, bleomycin, carboplatin, carmustine, chlorambucil, cisplatin, colaspase, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, daunorubicin, doxorubicin (adriamycine), epirubicin, etoposide, 5-fluorouracil, hexamethylmelamine, hydroxyurea, ifosfamide, irinotecan, leucovorin, lomustine, mechlorethamine, 6-mercaptopurine, mesna, methotrexate, mitomycin C, mitoxantrone, prednisolone, prednisone, procarbazine, raloxifen, streptozocin, tamoxifen, thioguanine, topotecan, vinblastine, vincristine, and vindesine.

Other cancer treatment agents suitable for use with the composition of the invention include but are not limited to those compounds acknowldeged to be used in the treatment of neoplastic diseases in *Goodman and Gilman's The Pharmacological Basis of Therapeutics* (Tenth Edition), editor Hardman et al., publ. by McGraw-Hill, pages 1389-1459, (2001), which is hereby incorporated by reference, such as aminoglutethimide, anastrazole, L-asparaginase, azathioprine, 5-azacytidine cladribine, busulfan, camptothecin, diethylstilbestrol, docetaxel, erythrohydroxynonyladenine, ethinyl estradiol, exemestane, 5-fluorodeoxyuridine, 5-fluorodeoxyuridine monophosphate, fludarabine phosphate, fluoxymesterone, flutamide, formestane, hydroxyprogesterone caproate, gemcitabine, idarubicin, IL-2, α-interferon, letrozole, medroxyprogesterone acetate, megestrol acetate, melphalan, mitotane, oxaliplatin, paclitaxel, pentostatin, N-phosphonoacetyl-L-aspartate

(PALA), plicamycin, semustine, teniposide, testosterone propionate, thiotepa, temozolomide, trimethylmelamine, uridine, vinorelbine and vorozole.

Other cancer treatment agents suitable for use with the composition of the invention include but are not limited to other anti-cancer agents such as epothilone.

For all regimens of use disclosed herein for compounds of formulae (I) or (II), the daily oral dosage regimen will preferably be from 0.01 to 200 mg/kg of total body weight. The daily dosage for administration by injection, including intravenous, intramuscular, subcutaneous and parenteral injections, and use of infusion techniques will preferably be from 0.01 to 200 mg/kg of total body weight. The daily rectal dosage regimen will preferably be from 0.01 to 200 mg/kg of total body weight. The daily vaginal dosage regimen will preferably be from 0.01 to 200 mg/kg of total body weight. The daily topical dosage regimen will preferably be from 0.1 to 200 mg administered between one to four times daily. The transdermal concentration will preferably be that required to maintain a daily dose of from 0.01 to 200 mg/kg. The daily inhalation dosage regimen will preferably be from 0.01 to 100 mg/kg of total body weight.

It will be appreciated by those skilled in the art that the particular method of administration will depend on a variety of factors, all of which are considered routinely when administering therapeutics. It will also be understood, however, that the specific dose level for any given patient will depend upon a variety of factors, including, but not limited to the activity of the specific compound employed, the age of the patient, the body weight of the patient, the general health of the patient, the gender of the patient, the diet of the patient, time of administration, route of administration, rate of excretion, drug combinations, and the severity of the condition undergoing therapy. It will be further appreciated by one skilled in the art that the optimal course of treatment, i.e., the mode of treatment and the daily number of doses of a compound of formulae (Ia) or (IIa) or a pharmaceutically acceptable salt thereof given for a defined number of days, can be ascertained by those skilled in the art using conventional treatment tests.

***Description of Preparative Methods***

**Abbreviations and Acronyms**

The following terms have the indicated meanings:

| | |
|---|---|
| AcOH | acetic acid |
| Boc | *tert*-butoxycarbonyl |
| Burgess reagent | (Methoxycarbonylsulfamoyl)triethylammonium hydroxide |
| CDI | 1,1'-carbonyldiimidazole |
| DBU | 1,8-Diazabicyclo[5.4.0]undec-7-ene |
| DMAP | 4-Dimethylaminopyridine |
| DMSO | dimethylsulfoxide |
| DMF | *N,N*-dimethylformamide |
| EDC | 1-[3-(Dimethylaminopropyl)]-3-ethylcarbodiimide hydrochloride |
| eq | equivalents |
| EtOAc | ethyl acetate |
| h | hour |
| Hex | hexanes |
| HPLC | high performance liquid chromatography |
| HOBT | hydroxybenzatriazolehydrate |
| IPA | isopropyl alcohol |
| LC | liquid chromatography |
| Me | methyl |
| MP | melting point |
| MS | mass spectra |
| NMR | nuclear magnetic resonance |
| NMP | 1-methyl-2-pyrrolidinone |
| PPA | polyphosphoric acid |
| rt | room temperature |
| TLC | thin layer chromatography |
| TFA | trifluoroacetic acid |
| THF | tetrahydrofuran |

**Experimental Section**

Analytical data ($^1$H NMR and LC-MS) for all compounds was in accordance with the described structure.

The term 'concentrated under reduced pressure' refers to use of a Buchi rotary evaporator at approximately 15 mm of Hg.

Thin-layer chromatography (TLC) was performed on Whatman® pre-coated glass-backed silica gel 60A F-254 250 μm plates. Visualization of plates was effected by one or more of the following techniques: (a) ultraviolet illumination, (b) exposure to iodine vapor, (c) immersion of the plate in a 10% solution of phosphomolybdic acid in ethanol followed by heating, and/or (d) immersion of the plate in a cerium sulfate solution followed by heating. Column chromatography (flash chromatography) was performed using 230-400 mesh EM Science® silica gel

Melting points (mp) were determined using a Thomas-Hoover melting point apparatus or a Mettler FP66 automated melting point apparatus and are uncorrected.

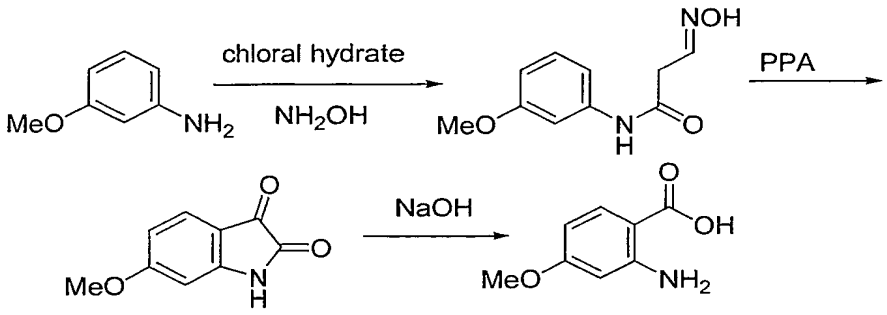
Proton ($^1$H) nuclear magnetic resonance (NMR) spectra were measured with a General Electric G*N*-Omega 300 (300 MHz) spectrometer with either $Me_4Si$ (δ 0.00) or residual protonated solvent ($CHCl_3$ δ 7.26; MeOH δ 3.30; DMSO δ 2.49) as standard. Carbon ($^{13}$C) NMR spectra were measured with a General Electric G*N*-Omega 300 (75 MHz) spectrometer with solvent ($CDCl_3$ δ 77.0; $d_3$-MeOD; δ 49.0; $d_6$-DMSO δ 39.5) as standard.

HPLC - electrospray mass spectra (HPLC ES-MS) were obtained using a Hewlett-Packard 1100 HPLC equipped with a quaternary pump, a variable wavelength detector set at 254 nm, a YMC pro C-18 column (2 x 23 mm, 120A), and a Finnigan LCQ ion trap mass spectrometer with electrospray ionization. Spectra were scanned from 120-1200 amu using a variable ion time according to the number of ions in the source. The eluents were A: 2% acetonitrile in water with 0.02% TFA and B: 2% water in acetonirile with 0.018% TFA. Gradient elution from 10% B to 95% over 3.5 minutes at a flowrate of 1.0 mL/min was used with an initial hold of 0.5 minutes and a final hold at 95% B of 0.5 minutes. Total run time

was 6.5 minutes. Alternative conditions are given for the parallel synthesis route in the experimental.

*A. Synthesis of Intermediates*

**A1. Preparation of 2-amino-4-methoxybenzoic acid.**




**Step 1**. Chloral hydrate (14.5 g, 87.7 mmol) was dissolved in water (190 mL) and then added to sodium sulfate (92.26 g, 650 mmol) in water (170 mL). *m*-Anisidine (10 g, 81.2 mmol) was dissolved in water (50 mL) with conc. HCl (7.0 mL) and added to the first mixture, a layer of brown oil formed on the top. Hydroxylamine hydrochloride (17.86 g, 256 mmol) was dissolved in water (80 mL) and added to the reaction mixture. The mixture was heated at 40 °C then warmed to 50 °C. Finally the mixture was heated to reflux for 10 min and the mixture was heated to 130 °C for 20 min. Cooled in water bath and then transferred to ice bath. The precipitate was collected by vacuum filtration and further washed with water (200 mL). The brown solid was vacuum dried to afford 13.5 g of (2E)-2-(hydroxyimino)-N-(3-methoxyphenyl)ethanamide (85%). MS (LC/MS) 195.1 (55%).

**Step 2**. (2E)-2-(Hydroxyimino)-N-(3-methoxyphenyl)ethanamide (13.5 g, 69.52 mmol) was mixed with polyphosphoric acid (135 g) and the mixture was heated at 55 °C for 6 h.. The reaction mixture was then poured into ice and an orange solid formed. The orange solid was recrystallized from acetone-petroleum ether to give 11.4 g of 6-methoxy-1H-indole-2,3-dione (93%). MS (LC/MS) 178.1 (100%).

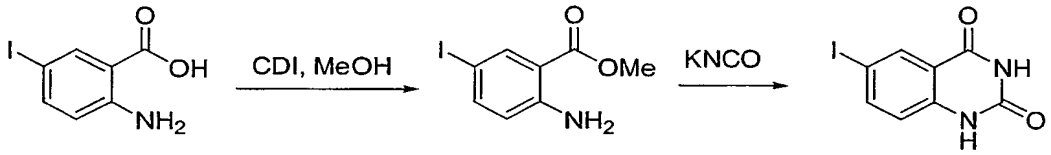
**Step 3**. 6-Methoxy-1H-indole-2,3-dione (5 g, 2.8 mmol) was dissolved in 5% NaOH solution. (180 mL). 35wt% $H_2O_2$ (67.5 mL, 7.05 mmol) was dissolved in water (88 mL) and added to the reaction mixture dropwise at 30-35 °C over 30 min. The reaction was then cooled to rt. 2M HCl (~200 mL) was added to the mixture to form a light yellow solid.

Filtration and drying the solid in the vacuum oven gave 2-amino-4-methoxybenzoic acid (66%). MS (LC/MS) 167.9 (100%).

**A2. Preparation of 6-bromo-2,4(1H,3H)-quinazolinedione**

2-Amino-5-bromobenzoic acid (3 g, 13.9 mmol) was mixed with urea (5.05 g, 83.3 mmol) and then heated to 180 °C. The mixture melted and gas evolution was seen, after 3 h the mixture solidified. The flask was cooled to rt and the brown solid was ground by mortar and suspended in water then stirred vigorously for 30 min. The suspension was then filtered and the solid was washed with acetone (10 mL) and water (150 mL). The solid was dried under vacuum to afford 3.14 g of 6-bromo-2,4(1H,3H)-quinazolinedione (94%). MS (LC/MS) 240.2 (100%).

**A3. Preparation of 6-iodo-2,4(1H,3H)-quinazolinedione**

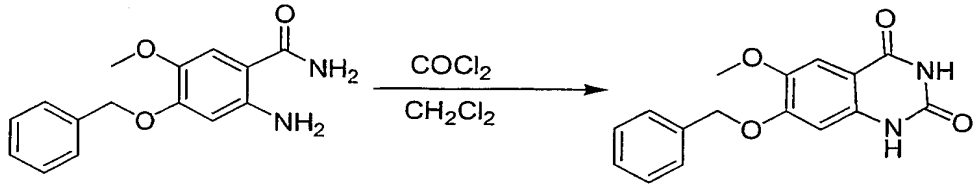


**Step 1.** 2-Amino-5-iodobenzoate acid (3 g, 11.4 mmol) was dissolved in THF and then 1,1'-carbonyldiimidazole (1.85 g, 11.4 mmol) was added. The mixture was heated at 60 °C for 2 days. The reaction was monitored by TLC. After starting material was consumed, MeOH (2 mL) was added and the mixture was heated at 70 °C for 1 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel column (100% $CH_2Cl_2$) to obtain 2.4 g of methyl 2-amino-5-iodobenzoate (76%). MS (GC/MS) 277.

**Step 2.** Methyl 2-amino-5-iodobenzoate (2.4 g, 8.66 mmol) was dissolved in AcOH (7.5 mL). Potassium cyanate was dissolved in water (1.5 mL) and added to the reaction mixture slowly. A precipitate formed immediately. The mixture was heated to 100 °C for 20 min and then mixture was added water and filtered by suction to afford a white solid. This white solid was dried under vacuum oven for 2 h. To this white solid was added MeOH (27 mL) to form a suspension. To this suspension, a solution of NaOH (406 mg) in water (5.4 mL)

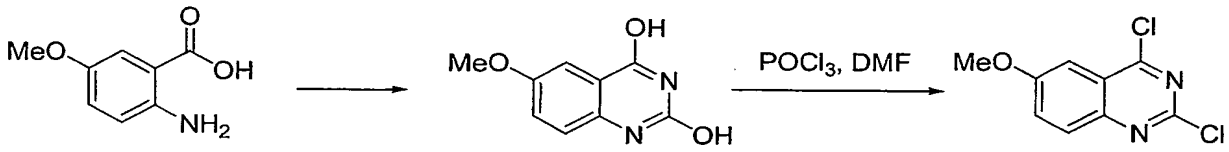
was added and the mixture was brought to reflux for 1 h. The reaction mixture was cooled and diluted with water (20 mL) and the pH was adjusted to pH 3 with 6 M HCl. Filtration gave 2.6 g of a colorless solid, 6-iodo-2,4(1H,3H)-quinazolinedione (100%).

**A4. Preparation of 7-(benzyloxy)-6-methoxy-2,4(1H,3H)-quinazolinedione.**




To a suspension of 4-benzyloxy-3-methoxybenzamide (*J.Med.Chem.* **1977**, Vol.20, p. 147.) (3.00 g, 11.02 mmol) in $CH_2Cl_2$ (50 mL) was added phosgene (5.5 mL), dropwise. The reaction was allowed to stir at room temperature for 4 days. The reaction was poured over saturated $NaHCO_3$ (500 mL). The resulting solid was collected by filtration and was dried *in vacuo* to afford 2.51 g of 7-(benzyloxy)-6-methoxy-2,4(1H,3H)-quinazolinedione (76%); $^1$H NMR (DMSO-$d_6$) 11.09 (s, 1H), 10.93 (s, 1H), 7.50-7.32 (m, 5H), 7.27 (s, 1H), 6.78 (s, 1H), 5.12 (s, 2H), 3.77 (s, 3H); ES MS $(M+H)^+$=299.2; TLC (50:50 Hexanes/EtOAc): $R_f$=0.72.

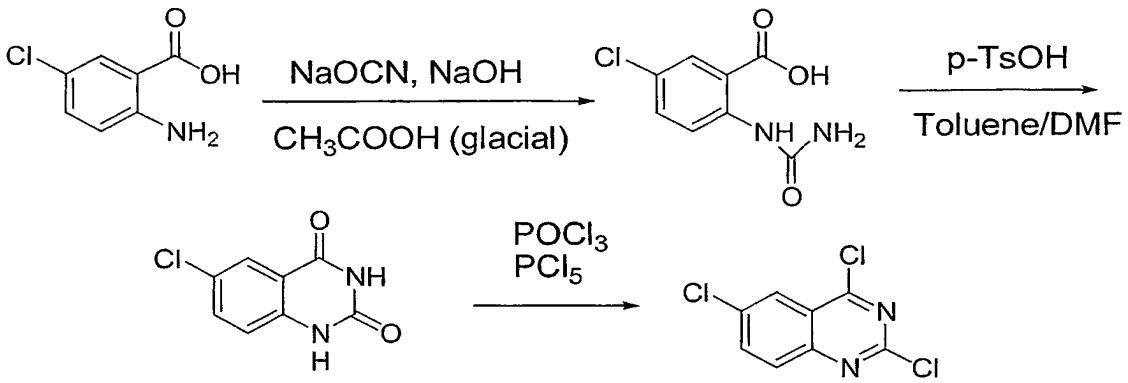
**A5. Preparation of 2, 4-dichloro-6-methoxyquinazoline.**




**Step 1**. To 2-amino-5-methoxylbenzoic acid (3 g, 17.9 5 mmol) was added 2N HCl (15 mL). After a precipitate formed, water (30 mL) was added to the mixture to form a suspension. A solution of sodium cyanate (1.75 g, 26.92 mmol) in water (20 mL) was added dropwise at rt over 15 min. Froth formed and after vigorously stirring, a pink suspension formed. After stirring for 4 h, the suspension was filtered and washed with water and ether and dried under reduced pressure. The solid was added to concentrated HCl (20 mL), and heated to 105 °C for 1 h. The suspension was then filtered, washed with water, and dried under reduced pressure to give 2.12 g 6-methoxy-2,4(1H,3H)-quinazolinedione (62%).MS (LC/MS) 193.2 (95%).

**Step 2.** To 6-methoxy-2,4(1H,3H)-quinazolinedione (2.13 g, 11.1 mmol) was added $POCl_3$ (8 mL) via syringe and DMF (1 mL). The mixture was heated to 105 °C for 18 h. $POCl_3$ was then removed under reduced pressure. To the solid was added ice and the mixture was stirred for 1 h. The suspension was filtered to afford a brown solid. The solid was purified by silica gel chromatography (1:1 EtOAc/Hex) to afford 592 mg of 2,4-dichloro-6-methoxyquinazoline (24%).MS (LC/MS) 229.3 (100%).

**A6. Synthesis of 2, 4, 6-trichloroquinazoline**



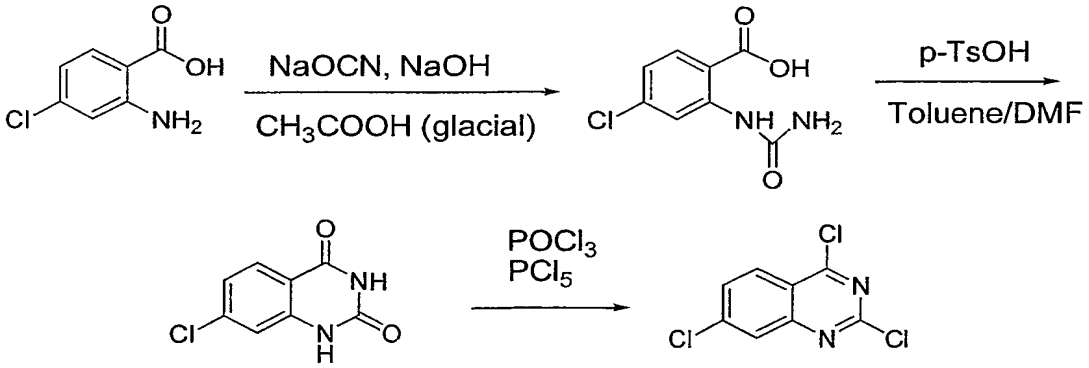

**Step 1.** To a suspension of 2-amino-5-chlorobenzoic acid (102.1g, 0.58 mol) in water (1.6 L) was added 5 M NaOH (160 mL). To the resulting solution was charged sodium cyanate (43.4 g, 0.64 mol) followed by glacial acetic acid (36.7 mL, 0.641 mol). The reaction mixture was stirred for a period of 14-16 h at rt, then filtered to remove some insoluble solid. To the brown solution was added 1 M HCl (1.5 L). The resulting precipitate was stirred rt for a period of 2-2.5 h then filtered and washed with water (2 x 666 mL). The solid was dried under vacuum at 50-60 °C for 48 h to obtain 124.6 g (99 %) of 2-[(aminocarbonyl)amino]-5-chlorobenzoic acid. $^1$HNMR (DMSO-$d_6$) δ 10.0 (1H, s), 8.43 (1H, d), 7.82 (1H, s), 7.50 (1H, dd), 6.65 (2H, br, s).

**Step 2.** A suspension of 2-[(aminocarbonyl)amino]-5-chlorobenzoic acid (35.0 g, 0.16 mol) and p-toluene sulfonic acid monohydrate (4.66 g, 0.024 mol) in a mixture of toluene (350 mL) and DMF (87.5 mL) was heated to reflux with an attached Dean stark apparatus for a period of 4-4.5 h. The reaction was judged complete by $^1$H NMR. The suspension was cooled to rt, filtered and the solid washed with toluene (150 mL). The damp solid was pulped in water (250 mL) for a period of 15-20 min. The material was filtered and washed with water (50 mL). The solid was dried under vacuum at 40-45 °C to yield 24.73 g (78%)

of 6-chloro-2,4(1H,3H)-quinazolinedione. $^1$HNMR (DMSO-$d_6$) δ 11.19 (1H, s), 11.02 (1H, s), 7.53 (1H, s), 7.40 (1H, d), 6.92 (1H, d).

**Step 3.** A mixture of 6-chloro-2,4(1H,3H)-quinazolinedione (24.0 g, 0.122 mol), $POCl_3$ (114 mL, 1.22 mol) and $PCl_5$ (56.2 g, 0.26 mol) was heated to reflux for a period of 3.5-4.0 h, when the reaction was judged complete by TLC (Eluent- 1:1 dichloromethane / hexanes). The reaction mixture was concentrated under vacuum to remove most of the $POCl_3$. The resulting solid was poured slowly into ice/water (1000/200 mL) and stirred vigorously for a period of one hour. The precipitate was filtered and the damp solid was pulped in water for 15-20 min. The solid was filtered, washed with water (100 mL) and dried under vacuum at rt for 24 h. The resulting crude product was suspended in ether (1.5 L) and stirred for a period of 1.0-1.5 h at rt. The insoluble particles were removed by celite filteration and the resulting solution was concentrated under reduced pressure to yield 25.45g (89 %) of the 2, 4, 6-trichloroquinazoline. $^1$HNMR (DMSO-$d_6$) δ 8.24 (1H, s), 8.15 (1H, d), 8.02 (1H, d). GCEI (8.15 min.) $M^+$- 232.

**A7. Preparation of 2, 4, 7-trichloroquinazoline.**



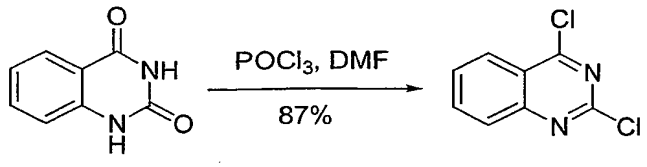

**Step 1.** To a suspension of 2-amino-4-chlorobenzoic acid (15.3 g, 0.087 mol) in water (245 mL) was added 5 M NaOH (24 mL, 0.12 mol). To the resulting solution was charged sodium cyanate (6.50 g, 0.096 mol) followed by glacial acetic acid (5.5 mL, 0.096 mol). The reaction mixture was stirred for a period of 14-16 h at rt, then filtered to remove some insoluble solid. To the yellow solution was added 1M HCl (225 mL). The resulting precipitate was stirred at rt for a period of 2-2.5 h then filtered and washed with water (2 x 100 mL). The solid was dried under vacuum at 50-60 °C for 48 h to obtain 17.6 g of 2-

[(aminocarbonyl)amino]-4-chlorobenzoic acid. $^1$HNMR (DMSO-$d_6$) δ 10.18 (1H, s), 8.53 (1H, s), 7.90 (1H, d), 6.97 (1H, dd), 6.70 (2H, br, s).

**Step 2.** A suspension of 2-[(aminocarbonyl)amino]-4-chlorobenzoic acid (14.0 g, 0.065 mol) and p-toluene sulfonic acid monohydrate (1.86 g, 0.01 mol) in a mixture of toluene (140 mL) and DMF (35 mL) was heated to reflux with an attached Dean stark apparatus for a period of 3.0 h. The reaction was judged complete by TLC (Eluent- 5:4:1 Hexanes/ethyl acetate/methanol). The suspension was cooled to rt, filtered and the solid washed with toluene (20 mL). The damp solid was pulped in water (80 mL) for a period of 15-20 min. The material was filtered and washed with water (20 mL). The solid was dried under vacuum at 40-45 °C to yield 7.64g (60 %) of 7-chloro-2,4(1H,3H)-quinazolinedione. $^1$HNMR (DMSO-$d_6$) δ 11.38 (1H, s), 11.21 (1H, s), 7.86 (1H, d), 7.19 (1H, s), 7.12 (1H, d).

**Step 3.** A mixture of 7-chloro-2,4(1H,3H)-quinazolinedione (7.5 g, 0.04 mol), $POCl_3$ (35.5 mL, 0.38 mol) and $PCl_5$ (17.5 g, 0.08 mol) was heated to reflux for a period of 3.0-3.5 h, when the reaction was judged complete by TLC (Eluent- 1:1 dichloromethane / hexanes). The reaction mixture was concentrated under vacuum to remove most of the $POCl_3$. The resulting solid was poured slowly into ice/water (350/75 mL) and stirred vigorously for a period of 1.5 h. The precipitate was filtered and the damp solid was pulped in water (80 mL) for 15-20 min. The solid was filtered, washed with water (30 mL) and dried under vacuum at rt for 24 h. to yield 8.5 g (96%) of 2, 4, 7-trichloroquinazoline. $^1$HNMR (DMSO-$d_6$) δ 8.27 (1H, d), 8.13 (1H, s), 7.89 (1H, d). GCEI (RT= 8.2 min) $M^+$- 232.

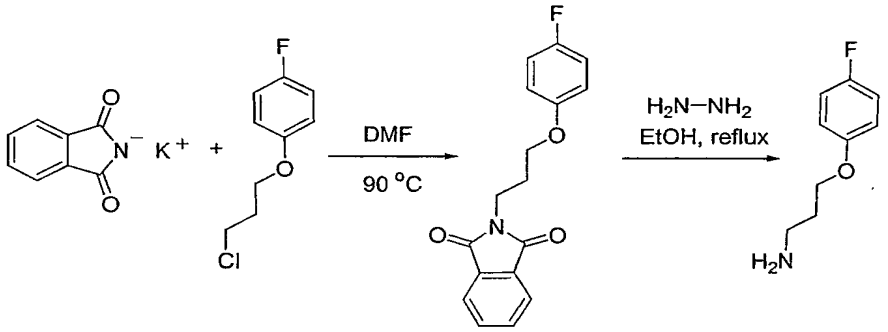
**A8. Preparation of 2, 4-dichloroquinazoline.**




A solution of dry DMF (4.0 mL) in phosphorous oxychloride (200 mL) was stirred at rt for 30 minutes, prior to its addition to a flask containing benzoyleneurea (50.00 g, 308.4 mmol). The suspension was heated to gentle reflux for 10 h, at which time, near-complete dissolution was achieved. The dark yellow contents were cooled to 55 °C and slowly added to cold (0 °C) water (2000 mL) that was vigorously stirred (the temperature of the aqueous

medium was not allowed to warm above 30 °C during the quench). A solid precipitated, which was stirred for 10 minutes and then filtered. The resultant cake was washed with water (3 x 350 mL) and then dried under high vacuum at 40 °C to provide 53.4 g of 2, 4-dichloroquinazoline (87%) as a pale-yellow solid. $^1$H-NMR (DMSO-$d_6$): δ 7.90 (ddd, J = 1.1, 7.0, 8.3 Hz, 1H, aromatic); 8.04 (dd, J = 1.1, 8.6 Hz, 1H, aromatic); 8.17 (ddd, J = 1.1, 7.0, 8.6 Hz, 1H, aromatic); 8.30 (dd, J = 1.1, 8.3 Hz, 1H, aromatic). Anal. Calcd for $C_8H_4N_2Cl_2 \cdot 0.1\ H_2O$: C, 47.84; H, 2.11; N, 13.95. Found: C, 47.91; H, 2.03; N, 13.94. Mass spectrum (HPLC/ES): m/e =199 (M+1).

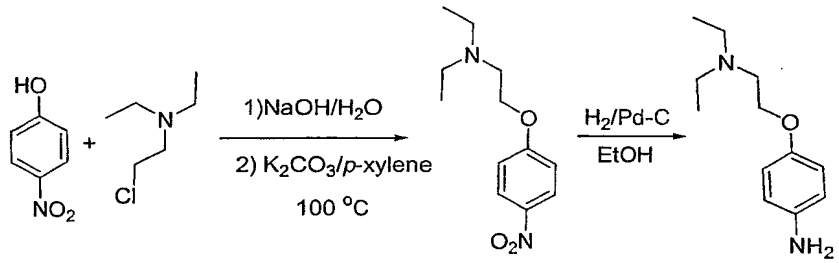
**A9. Preparation of 3-(4-fluorophenoxy)propylamine**




**Step 1**. 1-(3-Chloropropoxy)-4-fluorobenzene (1 eq) and phthalimide, potassium salt (1.2 eq) in a solution of DMF (1.0 M were magnetically stirred at 80 °C over a period of 18 h. The reaction was cooled, dissolved in $CH_2Cl_2$ and water and poured into a separatory funnel. The layers were separated and the aqueous was extracted with $CH_2Cl_2$ (3x). The combined organics were washed with 1N NaOH (2x), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The 2-[3-(4-fluorophenoxy)propyl]-1H-isoindole-1,3(2H)-dione was used without purification.

**Step 2.** The 2-[3-(4-fluorophenoxy)propyl]-1H-isoindole-1,3(2H)-dione (1 eq) and hydrazine hydrate (5 eq) in ethanol (0.1 M) were magnetically stirred at 80 °C over a period of 3 h. The reaction was cooled, the white precipitate was filtered off and washed with $CH_2Cl_2$. The combined filtrates were concentrated under reduced pressure. Methylene chloride was added to the crude residue and the solution was washed with water (2 x), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give 3-(4-fluorophenoxy)propylamine as a yellow oil which was used without further purification.

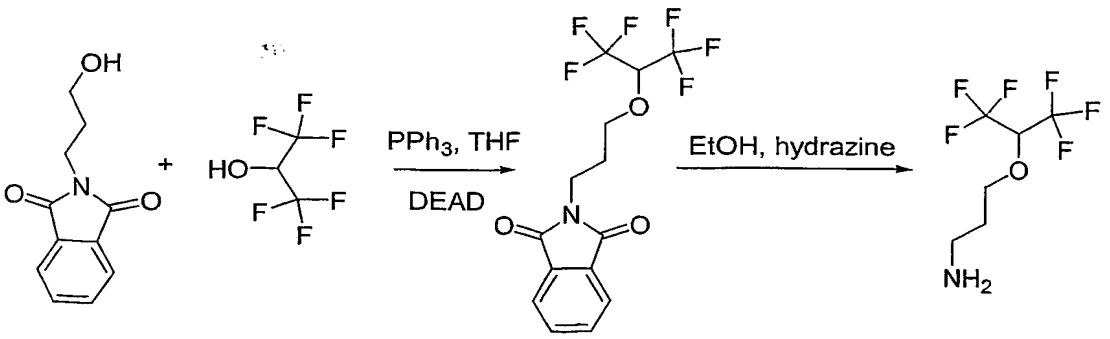
**A10. Synthesis of 4-[2-(diethylamino)ethoxy]aniline.**




**Step 1.** A slurry of 4-nitrophenol (1 eq) and NaOH pellets (1 eq) in $H_2O$ (6.8 M) was stirred for 10 min after which time *p*-xylene (1.4 M), $K_2CO_3$ (1.5 eq) and 2-diethylaminoethylchloride hydrochloride (1 eq) was added and the reaction heated to 100 °C for 4 h. The reaction was cooled to rt then concentrated under reduced pressure. The crude residue was dissolved in *p*-xylene and washed with 1N NaOH (2x) and $H_2O$ (1x). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to yield N,N-diethyl-2-(4-nitrophenoxy)ethanamine as a solid which was carried on without further purification.

**Step 2.** A solution of N,N-diethyl-2-(4-nitrophenoxy)ethanamine (1 eq) in ethanol (0.2 M) was added *via* syringe to a flask containing Palladium on carbon (10% wt). The reaction vessel was fitted with a balloon adapter and charged with hydrogen and evacuated three times until the reaction was under a $H_2$ atmosphere. The reaction was allowed to stir overnight and then purged with Ar and evacuated three times until an Ar atmosphere had been achieved. The reaction solution was filtered through a pad of Celite and washed with copious amounts of ethanol. The filtrate was concentrated under reduced pressure and afforded pure 4-[2-(diethylamino)ethoxy]aniline as an oil.

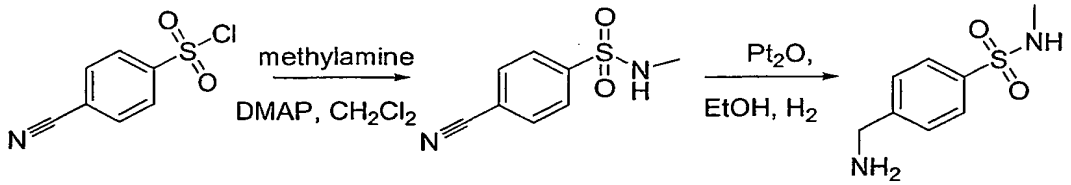
**A11. Preparation of 3-[2,2,2-trifluoro-1-(trifluoromethyl) ethoxy]propylamine.**



**Step 1:** To N-(3-Hydroxypropyl)phthalamide (0.10 g, 0.490 mmol, 1.0eq.) and hexafluoro-2-propanol (0.12 g, .730 mmol, 1.5eq.) in THF (4 mL) was added a mixture of triphenylphosphine (0.19 g, .730 mmol, 1.5 eq.) and diethylazodicarboxalate (0.13 g, 0.730 mmol, 1.5eq.) in THF (4 mL.) that was allowed to stir at 0 °C for 1h. The reaction was allowed to stir at rt for 3 h. It was concentrated under reduced pressure, taken up in ethyl acetate, washed with water, dried with magnesium sulfate, filtered and concentrated under reduced pressure. The crude mixture was purified by column chromatography (30% ethyl acetate/hexane) to give slightly impure 2-{3-[2,2,2-trifluoro-1-(trifluoromethyl) ethoxy]propyl}-1H-isoindole-1,3(2H)-dione that was used without further purification.

**Step 2:** To 2-{3-[2,2,2-trifluoro-1-(trifluoromethyl)ethoxy]propyl}-1H-isoindole-1,3(2H)-dione (1.0 g, 2.8 mmol, 1.0 eq.) in ethanol (10 mL) was added hydrazine hydrate (0.09 g, 2.8 mmol, 1eq.) and the reaction was allowed to stir at rt for 16 h. This was treated with 1N hydrochloric acid (5 mL) and the reaction was filtered washing with water. The filtrate was concentrated under reduced pressure and filtered to give 0.20 g of 3-[2,2,2-trifluoro-1-(trifluoromethyl)ethoxy]propylamine (32%).

**A12. Synthesis of 4-(aminomethyl)-N-methylbenzenesulfonamide.**

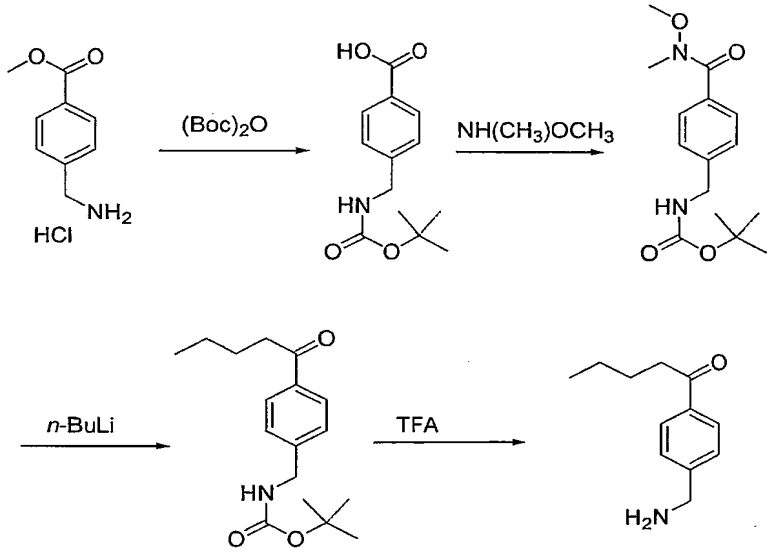



**Step 1:** To methylamine (2 M, 12.4 mL, 2.5eq.) and DMAP (0.24 g, 1.99 mmol., 0.2 eq.) in methylene chloride (15 mL.) was added 4-cyanobenzenesulfonyl chloride (2.0 g, 9.9 mmol., 1.0 eq.) portionwise at 0 °C. The reaction was allowed to warm rt and stir for 2h. The reaction was acidified with 2 N HCl to pH 1, and extracted with methylene chloride, dired with magnesium sulfate, filtered and concentated under reduced pressure to give 1.29 g of 4-cyano-N-methylbenzenesulfonamide (67%) as a colorless solid.

**Step 2:** To $PtO_2$ x $H_2O$ (0.13 g., 6.57 mmol., 1.0eq.) was added methanol (5 mL.) and HCl (0.13g, 7.88 mmol., 1.2 eq.) and 4-cyano-N-methylbenzenesulfonamide (1.29 g, 6.57 mmol., 1.0 eq.) and the reaction was placed under hydrogen gas (1 atm.) for 16 h. The reaction was

filtered and concentrated under reduced pressure to give 230 mg of 4-(aminomethyl)-N-methylbenzenesulfonamide (18%).

**A13. Preparation of 1-[4-(aminomethyl)phenyl]-1-pentanone.**




**Step 1.** A solution of methyl 4-(aminomethyl)benzoate hydrochloride (5 g, 26.65, 1 eq) in THF (50 mL) was treated with a solution of di-*tert*-butyl dicarbonate (14 g, 63.96 mmol, 2.4 eq) in THF (50 mL) dropwise. Triethylamine (11.14 mL, 8.1 g, 80 mmol, 3 eq) was added and the reaction was magnetically stirred over 16 hours.. Methylene chloride (100 mL) was added and the solution was washed with deionized water (100 mL), dried over magnesium sulfate and then filtered. The solution was concentrated in vacuo to yield a solid that was dissolved in methanol (100 mL) and treated dropwise with aquaeous NaOH (50% by wt, 5 mL) and magnetically stirred over 2 h. The reaction was then treated with aquaeous NaOH (1 N, 25 mL) and magnetically stirred over 30 min. Aqueous HCl (1N) was added until the reaction reached pH 7. Methanol was removed under reduced pressure , and the solid that formed was filtered to yield 4-{[(*tert*-butoxycarbonyl)amino]methyl}benzoic acid, which was used in the next step without further purification.

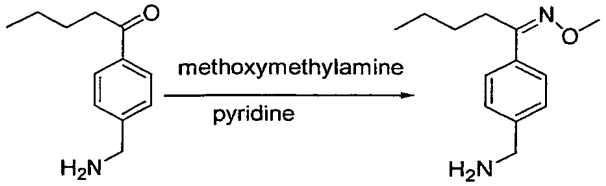
**Step 2** 4-{[(*tert*-Butoxycarbonyl)amino]methyl}benzoic acid (3g, 11.94 mmol, 1 eq) was dissolved in methylene chloride (50 mL) and treated with CDI (2.13 g, 13.13 mmol, 1.1 eq) and magnetically stirred over 20 min at rt. Dimethylhydroxylamine HCl (5.82 g, 59.70 mmol, 5 eq.) was added to this solution and magnetically stirred over 16 hours. Aqueous citric acid (10 % by wt., 100mL) were added and the organic sayer was separated and

successivively washed with deionized water (100 mL) and brine (100 mL), dried over magnesium sulfate and then filtered. The solution was concentrated *in vacuo*, and purified by column chromatography (50% Ethyl acetate:Hexanes) to yield *tert*-butyl 4-{[methoxy(methyl)amino]carbonyl}benzylcarbamate as a yellow oil.

**Step 3** To a previously cooled solution (0 °C, via ice/water bath) of *tert*-butyl 4-{[methoxy(methyl)amino]carbonyl}benzylcarbamate (0.5 g , 1.70 mmol, 1 eq) in THF (34 mL) under argon in an oven-dried flask, *n*-butyllithium (1.6 M in hexanes, 3.2 mL, 5.1 mmol, 3 eq) was added dropwise and the mixture was magnetically stirred for 1 hour. A solution of hydrogen chloride in ethyl ether and ethanol (16.6 mL of 2M HCl in ether and 3.4 mL of ethanol) were added and the mixture was immediately quenched dropwise with brine (100 mL). The organic layer was separated, dried over magnesium sulfate and then filtered. The solution was concentrated *in vacuo*, and purified by column chromatography (30% Ethyl acetate:hexanes) to yield 410 mg of tert-butyl 4-pentanoylbenzylcarbamate (83 %).

**Step 4** A solution of *tert*-butyl 4-pentanoylbenzylcarbamate (0.410 g) in methylene chloride (10 mL) was treated with TFA and magnetically stirred for 45 min. A saturated aqueous solution of sodium bicarbonate was added slowly followed by ethyl acetate (40 mL). The organic layer was separated, dried over magnesium sulfate and then filtered. The solution was concentrated under reduced pressure, resulting in 1-[4-(aminomethyl)phenyl]-1-pentanone which was used without any further purification.

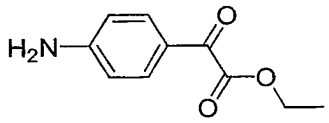
**A14. Preparation of of (1Z)-1-[4-(aminomethyl)phenyl]-1-pentanone O-methyloxime.**




A solution of 1-[4-(aminomethyl)phenyl]-1-pentanone (0.20 g, 1.05 mmol, 1 eq) and pyridine (0.25 mL) in ethanol (5 mL) was treated with methyloxylamine hydrochloride (0.175 g, 2.10 mmol, 2 eq) . The reaction was magnetically stirred at 88 °C over 6 h. The solution was cooled to rt, concentrated under reduced pressure, and purified by column chromatography (90% Ethyl acetate:methanol) to yield 30 mg of (1Z)-1-[4-

(aminomethyl)phenyl]-1-pentanone O-methyloxime (13%). LC/MS 220.5-221.5 at 2.03 min.

**A15. Preparation of ethyl (4-aminophenyl)(oxo)acetate.**

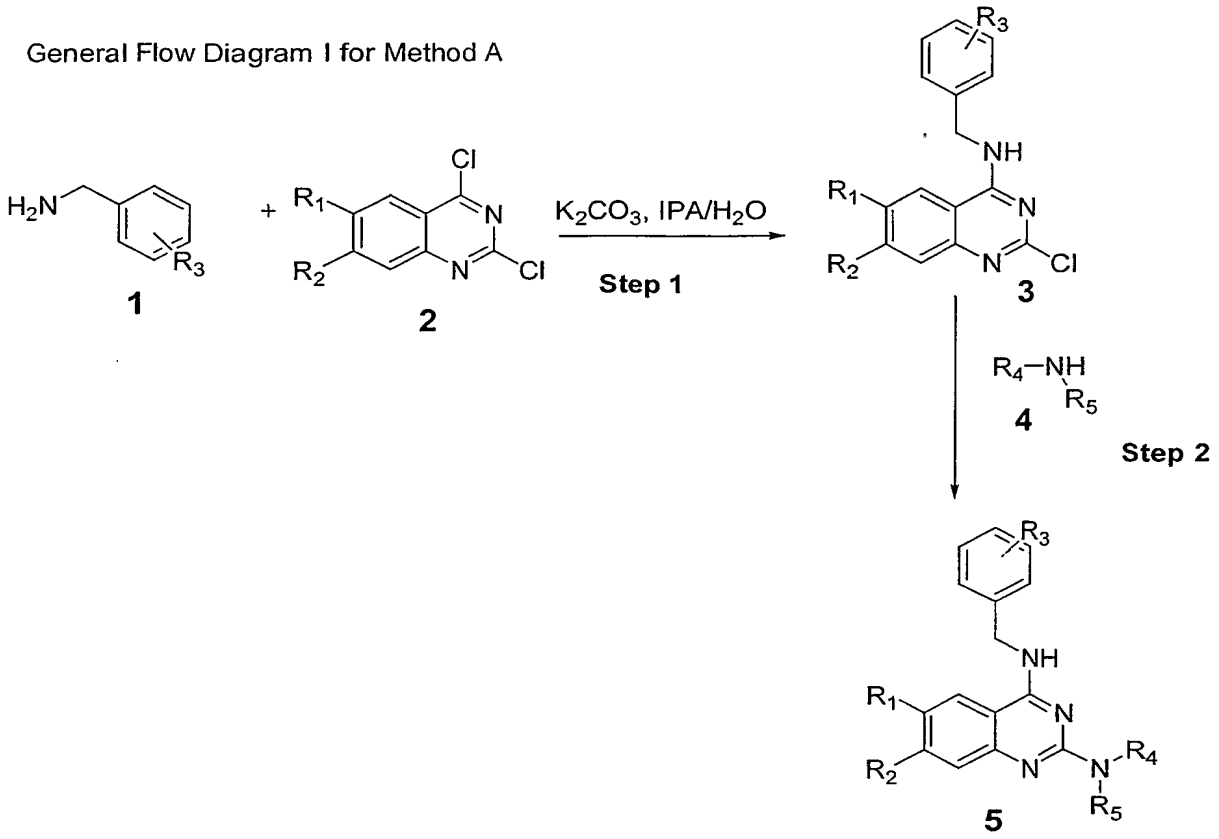


To a solution of ethyl 4-nitrophenylglyoxylate (3.60 g, 16.0 mmol) in glacial acetic acid (90 mL) was added iron powder (325 mesh) (7.20 g, 129.0 mmol) and the suspension stirred 16 h at rt. The solids were filtered off and washed with water (300 mL). This was extracted with Et2O (2 x 250 mL), and the organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to give a crude brown oil. Purification by silica gel chromatography (33% EtOAc/hexane) yielded the product as a yellow solid in 28% yield (870 mg, 4.506 mmol). ). HPLC/MS: [M+H]+obs = 194 @ tr = 2.89 min. (ESI+). 1H NMR (DMSO) d 7.55 (2H, d, J = 8.7 Hz), 6.59 (4H, d and bs overlapping, J = 8.7 Hz), 4.32 (2H, quartet, J = 7.2 Hz), 1.28 (3H, t, J = 7.2 Hz).

*B. Synthesis of Examples*

**B1. General Method**

General Flow Diagram I for Method A



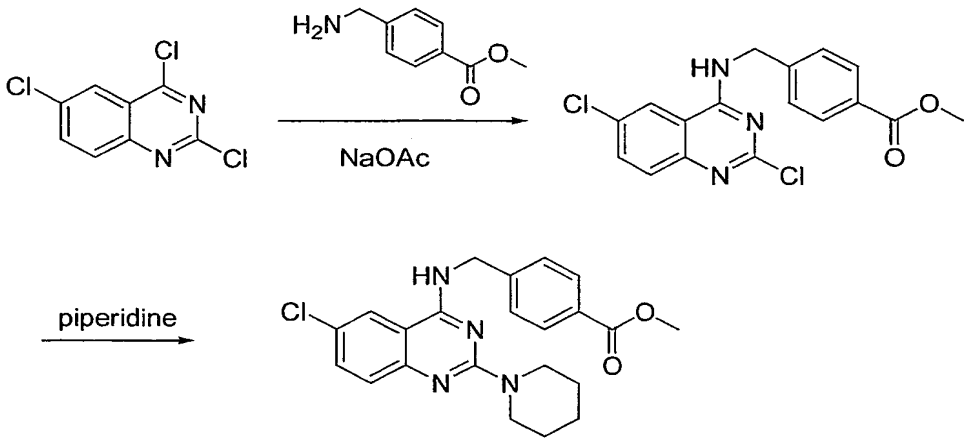

**Method A for Prolylpeptidase Compounds**

**Step 1.** Benzylamine **1 (General Flow Diagram I)** (1.1 eq) and potassium carbonate (3.5 eq) were added to a solution of quinazoline **2** (1.0 eq) in isopropyl alcohol and water (as a 2 to 1 ratio, 0.1 M) and were magnetically stirred at rt over a period of 16 h. The isopropyl alcohol was removed *in vacuo*. Ethyl acetate was added and this solution was washed with deionized water, dried over magnesium sulfate and then filtered. The solution was concentrated *in vacuo*, and purified by column chromatography to yield intermediate **3** as a white solid.

**Step 2.** Amine **4** (1.1 eq) and concentrated hydrochloric acid (catalytic) were added to a solution of intermediate **3** (1.0 eq) in *n*-butanol (0.1M) were magnetically stirred at 100 °C in a sealed tube over a period of 16 h. The excess *n*-butanol was removed under reduced pressure. Methylene chloride was added and the solution was washed with saturated aqueous

sodium bicarbonate solution, dried over magnesium sulfate and then filtered. The solution was concentrated *in vacuo*, and purified by column chromatography to yield compound **5**.

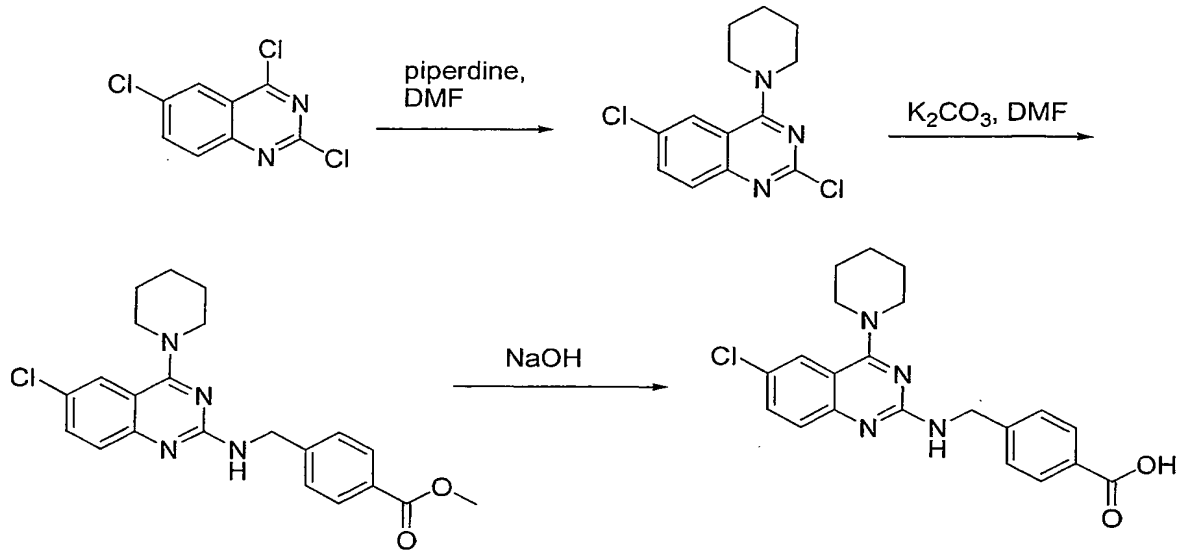
**B2. Example 1. Preparation of methyl 4-({[6-chloro-2-(1-piperidinyl)-4-quinazolinyl]amino}methyl)benzoate.**




**Step 1**. A suspension of 2,4,6-trichloroquinazoline (685 mg, 2.93 mmol), methyl 4-(aminomethyl)benzoate hydrochloride (651 mg, 3.28 mmol), and sodium acetate (722 mg, 8.80 mmol) in water (25 mL) was refluxed for 30 min vigorously. The white suspension is filtered through a coarse frit while still warm, and washed thoroughly with water (2 x 30 mL), then dried under $P_2O_5$ *in vacuo* to give 884 mg of methyl 4-{[(2,6-dichloro-4-quinazolinyl)amino]methyl}benzoate as a white solid in (83%). TLC: Rf = 0.25 (20% EtOAc/hexane); HPLC/MS: [M+H]+obs = 362 @ tr = 3.81 min. (ESI+).

**Step 2**. A suspension of methyl 4-{[(2,6-dichloro-4-quinazolinyl)amino] methyl}benzoate (850 mg, 2.347 mmol) in piperidine (3.00 g, 35.21 mmol) was stirred at 80 C under argon for 10 min. The reaction was diluted with water (50 mL) and extracted with EtOAc (3 x 100 mL). The organics were dried ($MgSO_4$) and concentrated in vacuo to give a yellow oil which crystallizes. This was purified by silica gel chromatography (10% EtOAc/hexane → 100% EtOAc) to give methyl 4-({[6-chloro-2-(1-piperidinyl)-4-quinazolinyl]amino}methyl)benzoate as a light yellow solid, crystallized from hexane, to give 746 mg (77%). TLC: Rf = 0.40(20% EtOAc/hexane); HPLC/MS: [M+H]+obs = 411 @ tr = 3.16 min. (ESI+).

**B3. Example 2. Preparation of 4-({[6-chloro-4-(1-piperidinyl)-2-quinazolinyl]amino} methyl)benzoic acid.**

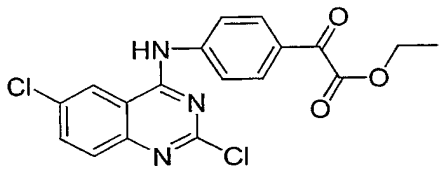



**Step 1**. To a suspension of 2,4,6-trichloroquinazoline (300 mg, 1.29 mmol) in dry DMF (10 mL) at 0 °C under argon was added piperidine (0.26 mL, 2.639 mmol) and the yellow suspension stirred at 0 °C for 30 min, then at rt for 16 h. The reaction was diluted with water (75 mL) and sat. $NaHCO_3$ (25 mL) and extracted with EtOAc (2 X 150 mL). The organics were washed with water (2 X 50 mL), dried ($MgSO_4$), and concentrated in vacuo to give a yellow solid. This was purified by silica gel chromatography (5% EtOAc/hexane) to give 2,6-dichloro-4-(1-piperidinyl)quinazoline as yellow crystals (from hexane) in 78% yield (269 mg, 0.953 mmol). TLC: Rf = 0.25 (10% EtOAc/hexane); HPLC/MS: [M+H]+obs = 282 @ tr = 3.98 min. (ESI+).

**Step 2**. A suspension of 2,6-dichloro-4-(1-piperidinyl)quinazoline (100 mg, 0.35 mmol), methyl 4-(aminomethyl)benzoate hydrochloride (105 mg, 0.523 mmol), and potassium carbonate (144 mg, 1.044 mmol) in dry DMF (5 mL) under argon was heated to 120 °C for 3 h. The reaction was quenched with water (100 mL) and extracted with EtOAc (2 x 150 mL). The organics were washed with water (50 mL), dried ($MgSO_4$), and concentrated under reduced pressure to give a yellow oil. The crude product was purified by silica gel chromatography (25-50% EtOAc/hexane) to give the product as a yellow foam solid in 38% yield (54 mg, 0.131 mmol). TLC: Rf = 0.17 (25% EtOAc/hexane); HPLC/MS: [M+H]+obs = 411 @ tr = 3.25 min. (ESI+).

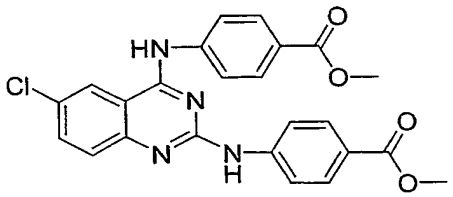
**Step 3.** A solution of methyl 4-({[6-chloro-4-(1-piperidinyl)-2-quinazolinyl]amino} methyl)benzoate (50 mg, 0.122 mmol) in methanol (5 mL) and 5 M NaOH (aq)(0.73 mL, 3.65 mmol) was stirred at rt for 24 h. The reaction was quenched by addition of 1 M HCl (aq)(3.70 mL), then diluted with Na/K tartrate/$NaHSO_4$ buffer at pH 4.5 (50 mL). This was extracted with EtOAc (2 X 150 mL) and the organic layers dried ($MgSO_4$) and concentrated in vacuo to give 35 mg of 4-({[6-chloro-4-(1-piperidinyl)-2-quinazolinyl]amino} methyl)benzoic acid as a colorless solid (73%). TLC: Rf = 0.18 (10% MeOH/EtOAc); HPLC/MS: [M+H]+obs = 397 @ tr = 3.06 min. (ESI+).

**B4. Preparation of ethyl {4-[(2,6-dichloro-4-quinazolinyl)amino] phenyl} (oxo)acetate.**



A suspension of 2,4,6-trichloroquinazoline (404 mg, 1.73 mmol), ethyl (4-aminophenyl) (oxo)acetate (485 mg, 2.51 mmol), and sodium acetate (287 mg, 3.50 mmol) in a mixture of THF (10 mL) and water (3.3 mL) was stirred at rt for 72 h, then refluxed for 3 h. The reaction was partitioned between water (50 mL) and EtOAc (100 mL) and the organics dried ($MgSO_4$) then the solvent was removed under reduced pressure. The crude oil (approx 600 mg), which contained approx 25% of the product by mass spec (150 mg, 0.38 mmol) was used without further purification. HPLC/MS: [M+H]+obs = 390 @ tr = 3.80 min. (ESI+).

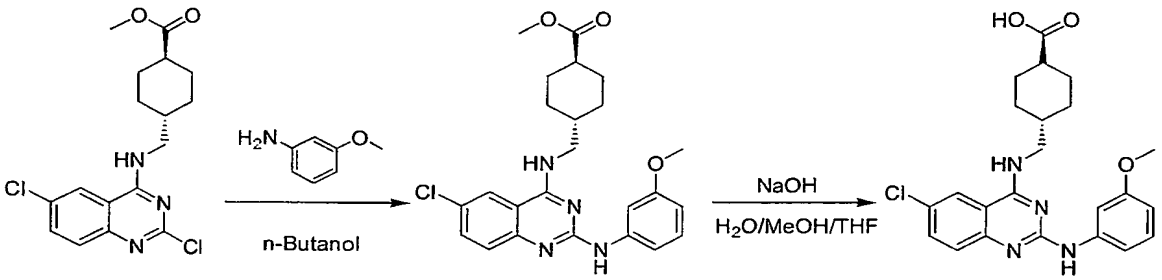
**B5. Preparation of methyl 4-[(6-chloro-2-{[4-(methoxycarbonyl)phenyl] amino}-4-quinazolinyl)amino]benzoate.**



A solution of 2,4,6-trichloroquinazoline (147 mg, 0.629 mmol) and methyl 4-aminobenzoate (128 mg, 0.850 mmol) in absolute ethanol (7 mL) was refluxed for 1 h. The resulting solid was filtered off while the reaction was still warm, then washed with hot ethanol to give the crude product. Recrystallization from methanol/EtOAc methyl gave 104 mg of 4-[(6-chloro-2-{[4-(methoxycarbonyl)phenyl]amino}-4-quinazolinyl) amino] benzoate as a colorless

solid in (36%). HPLC/MS: [M+H]+obs = 463 @ tr = 3.44 min. (ESI+). 1H NMR (DMSO) d 10.44/10.21 (1H ea, 2 b s), 8.65 (1H, s), 8.0 (4H, m), 7.85 (5H, m), 7.62 (1H, d, J = 9 Hz), 3.86/3.82 (3H ea, 2 s).

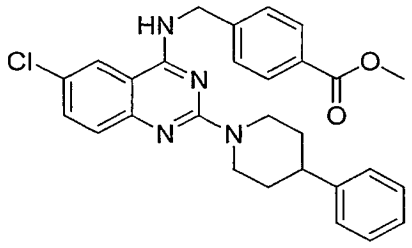
**B6. Example 3. Preparation of *trans*4-[({6-chloro-2-[(3-methoxyphenyl)amino]-4-quinazolinyl} amino)methyl]cyclohexane carboxylic acid.**




**Step 1.** A solution of *m*-anisidine (0.017 g, 0.14 mmol) and *trans*-methyl 4-{[(2,6-dichloro-4-quinazolinyl)amino]methyl}cyclohexanecarboxylate (0.050 g, 0.14 mmol) in *n*-butanol (2 mL) was heated at reflux overnight. The reaction was cooled to rt and the *n*-butanol was concentrated under reduced pressure. The crude product was purified by preparative HPLC ($C_{18}$ ODS, 10-90% $CH_3CN/H_2O$ 0.1% TFA) and dried *in vacuo* to afford 53 mg of *trans*-methyl 4-[({6-chloro-2-[(3-methoxyphenyl)amino]-4-quinazolinyl} amino)methyl]cyclohexanecarboxylate (85%); mp = 216-218 °C; ES MS $(M+H)^+$= 455.5; TLC ($CH_2Cl_2$/MeOH, 95:5): $R_f$ = 0.64.

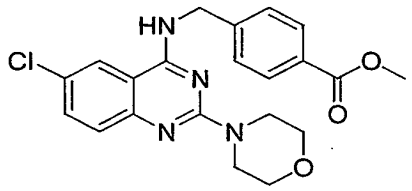
**Step 2.** A solution of *trans*-methyl 4-[({6-chloro-2-[(3-methoxyphenyl)amino]-4-quinazolinyl}amino)methyl]cyclohexanecarboxylate (0.02 g, 0.04 mmol) and 1N NaOH (0.04 mL) in MeOH/$H_2O$/THF (1.5 mL/0.25 mL/0.25 mL) was stirred at room temperature overnight then at 40 °C over 6 days. The reaction was cooled rt and the volatiles were removed under reduced pressure. The pH was adjusted to pH 6 with the addition of 1N HCl, the resulting solid was collected by filtration, and was dried *in vacuo* to afford *trans*-4-[({6-chloro-2-[(3-methoxyphenyl)amino]-4-quinazolinyl}amino) methyl]cyclohexane carboxylic acid (0.011 g, 0.026 mmol; 59% yield); mp = 258-261 °C, ES MS $(M+H)^+$=441.5; Ret. Time (HPLC)= 2.76 min.

**B7. Example 4. Preparation of methyl 4-({[6-chloro-2-(4-phenyl-1-piperidinyl)-4-quinazolinyl]amino}methyl)benzoate.**



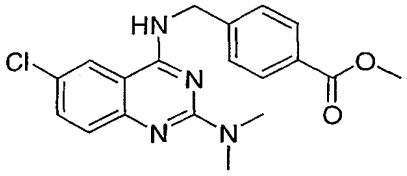
A solution of methyl 4-{[(2,6-dichloro-4-quinazolinyl)amino]methyl}benzoate (100 mg, 0.28 mmol) and 4-phenylpiperidine (213 mg, 1.323 mmol) in dry DMF (6 mL) was stirred under argon at rt for 11 h. The reaction was quenched with water (75 mL) and sat. $NaHCO_3$ (25 mL) and extracted with EtOAc (2 x 200 mL). The organics were washed with water (50 mL), dried ($MgSO_4$), and concentrated under reduced pressure to give a yellow oil. The crude product was purified by silica gel chromatography (20% EtOAc/hexane) to give methyl 4-({[6-chloro-2-(4-phenyl-1-piperidinyl)-4-quinazolinyl]amino}methyl)benzoate as a colorless oil. A colorless solid was obtained by crystallization in minimal $CH_2Cl_2$ with added hexane over 8 h. TLC: Rf = 0.40 (25% EtOAc/hexane); HPLC/MS: [M+H]+obs = 487 @ tr = 3.35 min. (ESI+).

**B8. Preparation of methyl 4-({[6-chloro-2-(4-morpholinyl)-4-quinazolinyl] amino}methyl)benzoate.**



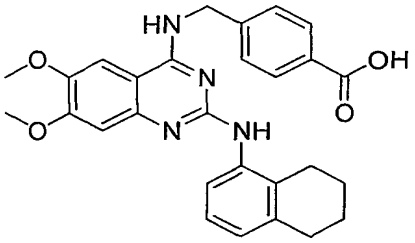
A suspension of 4-{[(2,6-dichloro-4-quinazolinyl)amino]methyl}benzoate (100 mg, 0.28 mmol) and morpholine (1.08 mL, 12.42 mmol) was stirred at rt for 24 h under argon. The reaction was diluted with water (50 mL) and sat $NaHCO_3$ (2 mL) and extracted with EtOAc (2 x 100 mL). The organics were dried ($MgSO_4$) and concentrated under reduced pressure to give a light yellow solid. This was dissolved in minimal $CH_2Cl_2$ (2 mL) and crystallized with added hexane to give 99 mg of methyl 4-({[6-chloro-2-(4-morpholinyl)-4-quinazolinyl] amino}methyl)benzoate as a colorless solid (87%). TLC: Rf = 0.55 (50% EtOAc/hexane); HPLC/MS: [M+H]+obs = 413 @ tr = 2.84 min. (ESI+).

**B9. Preparation of methyl 4-({[6-chloro-2-(dimethylamino)-4-quinazolinyl] amino}methyl)benzoate.**



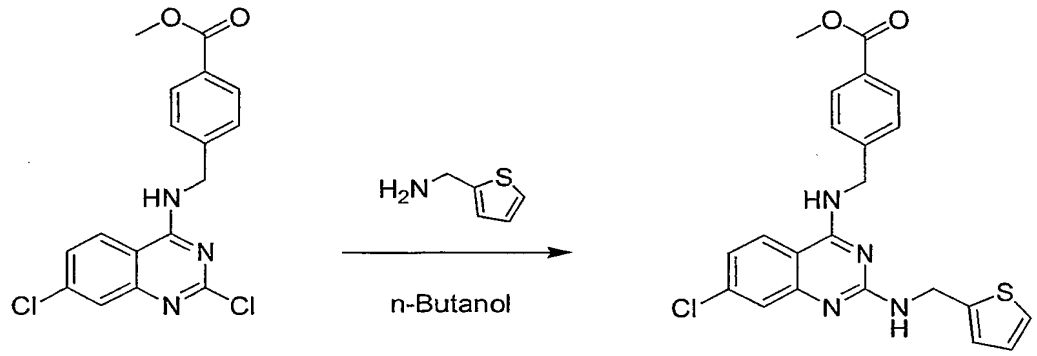
A solution of 4-{[(2,6-dichloro-4-quinazolinyl)amino]methyl}benzoate (100 mg, 0.28 mmol) and 2-aminopyridine (131 mg, 1.39 mmol) in dry DMF (2.5 mL) was heated in a sealed vial at 100 °C for 24 h, then at 150 °C for 6 h. The reaction was diluted with water (75 mL) and extracted with EtOAc (2 x 150 mL). The organics were washed with water (2 x 50 mL), dried ($MgSO_4$), and concentrated under reduced pressure to give a yellow oil. Purification by silica gel chromatography (33% EtOAc/hexane) afforded 45 mg of methyl 4-({[6-chloro-2-(dimethylamino)-4-quinazolinyl] amino}methyl)benzoate as yellow crystals in (44%). TLC: Rf = 0.60 (50% EtOAc/hexane); HPLC/MS: [M+H]+obs = 371 @ tr = 2.94 min. (ESI+).

**B10. Example 5. Preparation of 4-({[6,7-dimethoxy-2-(5,6,7,8-tetrahydro-1-naphthalenylamino)-4-quinazolinyl]amino}methyl)benzoic acid.**



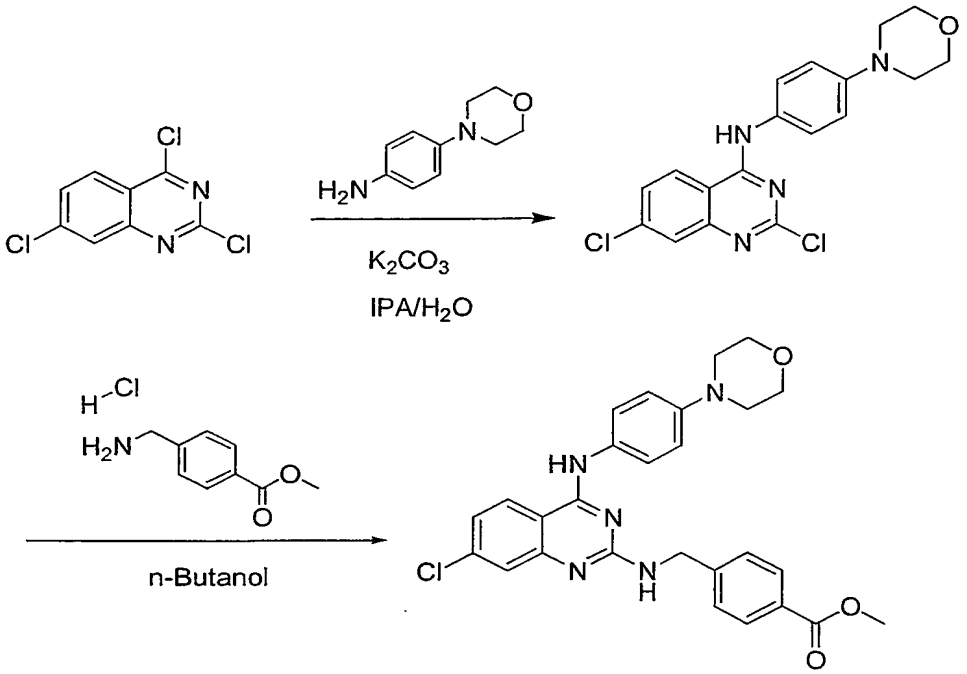
4-{[(2-Chloro-6,7-dimethoxy-4-quinazolinyl)amino]methyl}benzoic acid (400 mg, 1.07 mmol) is heated in neat 5,6,7,8-tetrahydro-1-naphthalenamine (2 mL, 13.6 mmol) with catalytic conc. HCl added (4 drops) at 140 °C for 5 h. The crude reaction was purified directly by silica gel chromatography (33% MeOH/EtOAc) to give a residue which was crystallized in methanol to give 22 mg of 4-({[6,7-dimethoxy-2-(5,6,7,8-tetrahydro-1-naphthalenylamino)-4-quinazolinyl]amino}methyl)benzoic acid as a colorless solid (4%). HPLC/MS: [M+H]+obs = 485 @ tr = 2.46 min. (ESI+). 1H NMR (DMSO) d 12.75 (1H, b s), 8.42/7.64 (1H ea, 2 b s), 7.86/7.37 (2H ea, d, J = 7.8 Hz), 7.62 (1H, s), 7.45 (1H, d, J = 8.4 Hz), 6.94 (1H, t, J = 7.5 Hz), 6.75 (2H, s overlapping with d, J = 7.2 Hz), 4.72 (2H, d, J = 9 Hz), 3.82/3.81 (3H ea, 2 s), 2.72/2.58 (2H ea, 2 m), 1.63 (4H, m).

**B11. Example 6. Preparation of methyl 4-[({7-chloro-2-[(2-thienylmethyl)amino]-4-quinazolinyl}amino)methyl]benzoate.**




A solution of 2-thienylmethylamine (0.031 g, 0.28 mmol) and methyl 4-{[(2,7-dichloro-4-quinazolinyl)amino]methyl}benzoate (0.100 g, 0.28 mmol) in *n*-butanol (4 mL) was heated to reflux for 18 h. The reaction was cooled to rt and the *n*-butanol concentrated under reduced pressure. The crude product was purified by preparative HPLC ($C_{18}$ ODS, 10-90% $CH_3CN/H_2O$ 0.1% TFA) and dried *in vacuo* to afford 61 mg of methyl 4-[({7-chloro-2-[(2-thienylmethyl)amino]-4-quinazolinyl}amino)methyl]benzoate (50%); mp = 176-178 °C; ES MS $(M+H)^+$= 439.9; Ret. Time (HPLC)= 2.25 min.

**B12. Example 7. Preparation of methyl 4-{[(7-chloro-4-{[4-(4-morpholinyl)phenyl] amino}-2-quinazolinyl)amino]methyl}benzoate.**

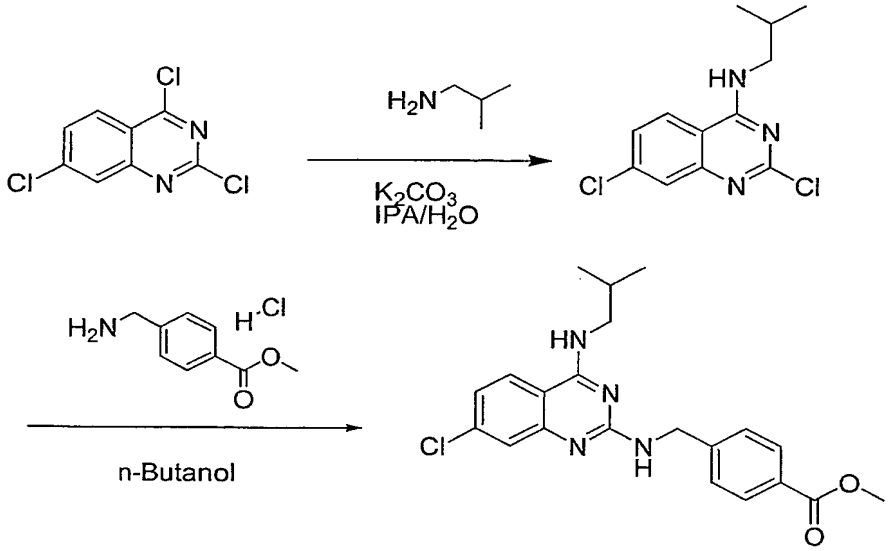



**Step 1.** A mixture of 2,4,7-trichloroquinazoline (0.20 g, 0.86 mmol), 4-(4-morpholinyl)phenylamine (0.229 g, 1.28 mmol), potassium carbonate (0.355 g, 2.57 mmol) in IPA/water (5.3 mL/2.7 mL) was heated at 60° C for 18 h. The reaction was cooled to rt and the solvent was removed under reduced pressure. The pH was adjusted to 6 with the addition of 1N HCl and the mixture was concentrated *in vacuo*. The crude mixture was purified by preparative HPLC ($C_{18}$ ODS, 30-90% $CH_3CN/H_2O$ 0.1% TFA) to afford 2,7-dichloro-N-[4-(4-morpholinyl)phenyl]-4-quinazolinamine (0.100 g, 0.293 mmol; 33% yield); $^1$H NMR (DMSO-$d_6$) 10.22 (s, 1H), 8.54 (d, $J$= 8.8 Hz, 1H), 7.73 (d, $J$= 2.0 Hz, 1H), 7.69-7.64 (m, 1H), 7.57 (d, $J$ = 8.8 Hz, 2H), 7.03 (d, $J$ = 8.8 Hz, 2H), 3.78-3.70 (m, 4H), 3.18-3.10 (m, 4H); ES MS $(M+H)^+$=375.2; TLC (50:50 Hexanes/EtOAc): $R_f$=0.34.

**Step 2.** A solution of methyl 4-(aminomethyl)benzoate (0.027 g, 0.13 mmol) and 2,7-dichloro-N-[4-(4-morpholinyl)phenyl]-4-quinazolinamine (0.050 g, 0.13 mmol) in *n*-butanol (1 mL) was heated to reflux for 18 h. The reaction was cooled rt and the *n*-butanol was removed under reduced pressure. The crude product was purified by preparative HPLC ($C_{18}$ ODS, 30-90% $CH_3CN/H_2O$ 0.1% TFA) and dried *in vacuo* to afford 19 mg of methyl 4-{[(7-

chloro-4-{[4-(4-morpholinyl)phenyl]amino}-2-quinazolinyl)amino]methyl} benzoate (24%); mp = 95-99 °C; ES MS $(M+H)^+$= 504.4; TLC (90:10 $CH_2Cl_2$/MeOH): $R_f$=0.65.

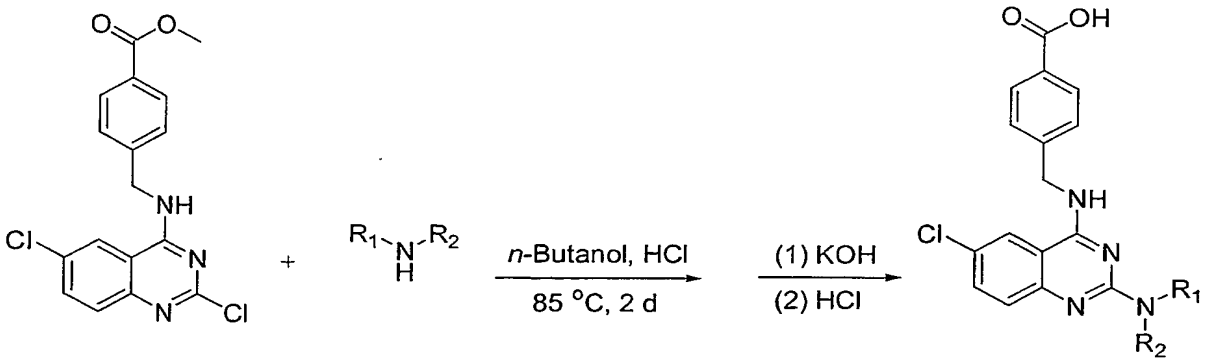
**B13. Example 8. Preparation of methyl 4-({[7-chloro-4-(isobutylamino)-2-quinazolinyl]amino}methyl)benzoate.**




**Step 1**. A mixture of 2, 4, 7-trichloroquinazoline (0.125 g, 0.54 mmol), *iso*-butyl amine (0.059 g, 0.080 mmol), and potassium carbonate (0.222 g, 1.61 mmol) in IPA/water (2.7 mL/1.3 mL) was heated at 60 °C for 18 h. The reaction was cooled to rt and the volatiles were removed under reduced pressure. The pH was adjusted to pH 6 with the addition of 1N HCl and the resulting solid was collected by filtration. The solid was dried *in vacuo* to afford 130 mg of 2,7-dichloro-N-isobutyl-4-quinazolinamine (90%); $^1$H NMR (DMSO-I) 8.96 (t, $J$ = 5.3 Hz, 1H), 8.37 (d, $J$ = 9.1 Hz, 1H), 7.65 (d, $J$ = 2.3 Hz, 1H), 7.57 (dd, $J$ = 2.4 Hz, 8.8 Hz, 1H), 3.30 (dd, $J$ = 5.9 Hz, 7.0 Hz, 2H), 2.01 (sept, $J$ = 7.0 Hz, 1H), 0.90 (d, $J$ = 6.6 Hz, 6H); ES MS $(M+H)^+$=270.1; TLC (50:50 Hexanes/EtOAc): $R_f$=0.82.

**Step 2.** A solution of methyl 4-(aminomethyl)benzoate hydrochloride (0.037 g, 0.19 mmol) and 2,7-dichloro-N-isobutyl-4-quinazolinamine (0.050 g, 0.19 mmol) in *n*-butanol (1 mL) was heated at reflux for 18 h. The reaction was cooled to rt and the *n*-butanol was removed *in vacuo*. The crude product was purified by preparative HPLC ($C_{18}$ ODS, 30-90% $CH_3CN/H_2O$ 0.1% TFA) and dried *in vacuo* to afford 13 mg of methyl 4-({[7-chloro-4-(isobutylamino)-2-quinazolinyl]amino}methyl)benzoate (13%); mp = 182-185 °C; ES MS $(M+H)^+$= 399.5; TLC (90:10 $CH_2Cl_2$/MeOH): $R_f$=0.63.

**B14. General Procedure for Parallel Synthesis**




The following solutions were prepared prior to use:

1. 2,5-dichloro-4-(4-methoxycarbonylbenzylamino)-quinazoline solution in *n*-butanol (0.02 mmol/200 μL)
2. $HNR_1R_2$ (primary or secondary amine) solution in n-butanol (0.024 mmol/200 μL)
3. 4 *N* potassium hydroxide solution in methanol and water (1:1)

To a 1-mL well in a 96-well Robbins FlexChem™ reaction block, 200 μL of 2,5-dichloro-4-(4-methoxycarbonylbenzylamino)-quinazoline (0.02 mmol) and 200 μL of amine (0.024 mmol) were dispensed. *n*-Butanol (95 μL) and 1.0 *M* hydrochloric acid in diether ether (5 μL) were added to each well. The plate was sealed with a rubber septum sheet, and rotated in a Robbins oven at 85 °C for 2 days. After allowing the reaction block to cool to room temperature, the septum was removed and the reaction mixture was filtered into a 2-mL 96-well collection plate, followed by washing 3 times with 200 μL MeOH. The solvent was evaporated under reduced pressure by using a multiple sample evaporator (GeneVac™).

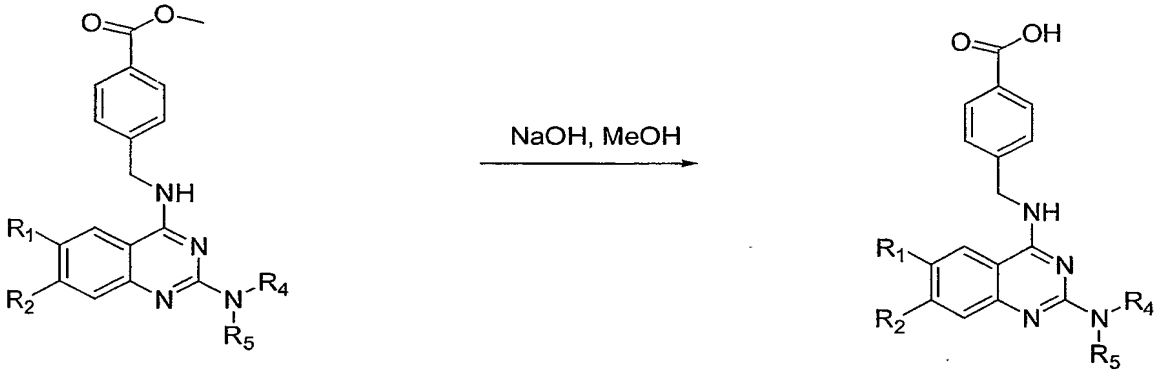
The residue was redissolved in 500 μL MeOH and transferred to a 1-mL well in a 96-well Robbins FlexChem™ reaction block. 4 *N* Potassium hydroxide (50 μL) was added to each well. The plate was sealed with a rubber septum sheet, and rotated in a Robbins oven at 60 °C for overnight. After allowing the reaction block to cool to room temperature, the septum was removed and 110 μL of 2 *N* Hydrochloric acid was added to each well. The reaction mixture was filtered into a 2-mL 96-well collection plate, followed by washing 3 times with 200 μL MeOH. The solvent was evaporated under reduced pressure (GeneVac). The residue was redissolved in 1 mL dichloromethane and filtered through a 2-mL well in a 96-well Robbins FlexChem™ reaction block into a 2-mL 96-well collection plate. The solvent was

evaporated under reduced pressure (GeneVac). The formation of desired products was confirmed by LC-MS analyses.

HPLC conditions for parallel synthesis analysis: A YMC Pro C-18 column (2 x 23mm, 120 A) was used, and the eluents were A: 2% acetonitrile in water with 0.02% TFA and B: 2% water in acetonitrile with 0.02% TFA. Elution conditions consisted of a flow rate of 1.5 mL/min with an initial hold at 10% B for 0.5 minutes, followed by gradient elution from 10% B to 90% B over 3.5 minutes, followed by a final hold at 90% B for 0.5 minutes. Total run time was 4.8 minutes.

*C. Modification of Examples*

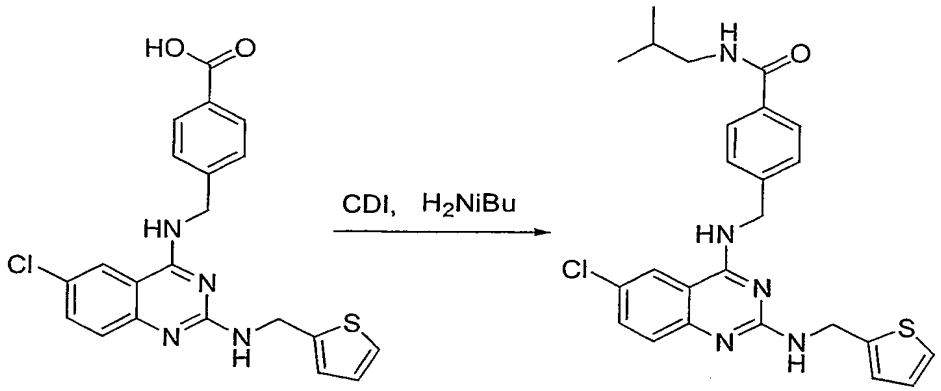
**C1. General Method for Hydrolysis of Ester.**




**6** **7**

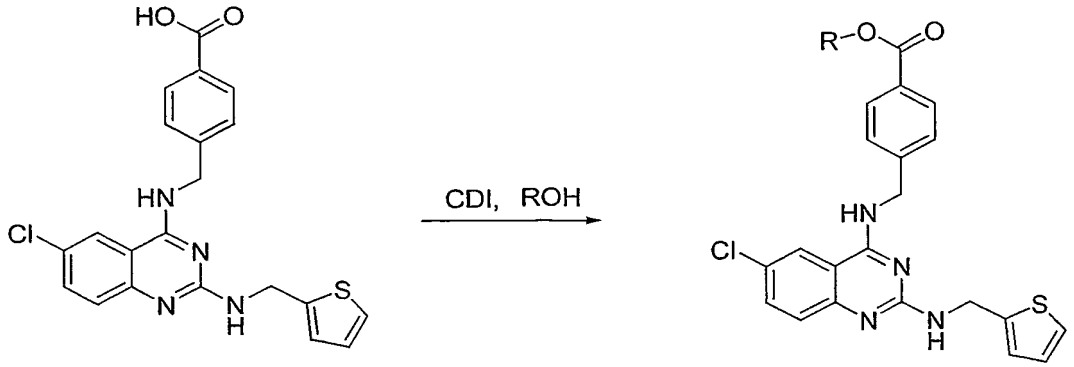
An excess of aqueous sodium hydroxide (1N) was added to a solution of ester **6** in methanol (0.1-0.05 M). The mixture was magnetically stirred at room temperature for 2 hours. The mixture was adjusted to pH 7 with aqueous hydrochloric acid (1N) and methanol was removed under reduced pressure. The resulting solid was filtered, rinsed with deionized water, and dried *in vacuo* to yield **2** as a solid.

**C2. Example 9. Preparation of 4-[({6-chloro-2-[(2-thienylmethyl)amino]-4-quinazolinyl}amino)methyl]-N-isobutylbenzamide.**



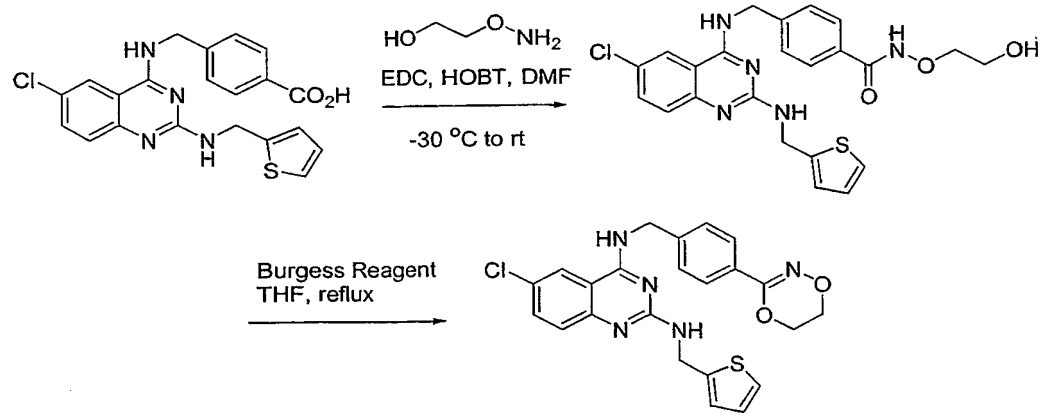

A heterogeneous solution of 4-[({6-Chloro-2-[(2-thienylmethyl)amino]-4-quinazolinyl} amino)methyl]benzoic acid (100 mg, 0.24 mmol, 1.0 eq) in 4 mL of DMF was magnetically stirred at 75 °C until homogeneous. 1,1'-Carbonyldiimidazole (38 mg, 0.24 mmol, 1.0 eq) was added and were heated at 75°C for 2 h. The corresponding amine (4.8 mmol, 20 eq) was added and the reaction was heated at 60°C over a period of 16 h. The reaction was cooled to rt and poured into 25 mL of water. The aqueous layer was extracted 3 x 20 mL dichloromethane. The organic layers were combined, washed with 30 mL of brine, dried over magnesium sulfate, and the solvent was removed under reduced pressure. The residue was purified via preparatory HPLC (HPLC method: C18 ODS, 10-90% $CH_3CN/H_2O$ 0.1%TFA) to give 4-[({6-chloro-2-[(2-thienylmethyl)amino]-4-quinazolinyl}amino)methyl]-N-isobutylbenzamide. **$^1$H NMR** (DMSO-$d_6$) 8.26 (s, 1H), 7.79-7.76 (m, 3H), 7.46-7.43 (m, 3H), 7.23 (s, 1H), 6.90 (m, 2H), 4.88 (s, 2H), 4.80 (s, 2H), 3.18 (d, $J$=6.7 Hz, 2 H), 1.94-1.90 (sept, $J$=6.8 Hz, 1H), 0.95 (d, $J$=6.3 Hz, 6H); **MS** (ES) 480.4 $(M+H)^+$; **TLC** (100 % ETOAC) Rf = 0.44.

**C3. General Method for Synthesis of Esters**




A heterogeneous solution of 4-[({6-Chloro-2-[(2-thienylmethyl)amino]-4-quinazolinyl} amino)methyl]benzoic acid (100 mg, 0.24 mmol, 1.0 eq) in 4 mL of DMF was magnetically stirred at 75°C until homogeneous. 1,1'-Carbonyldiimidazole (38 mg, 0.24 mmol, 1.0 eq) was added and the reaction was heated at 75°C for 1 h. The corresponding alcohol (4.8 mmol, 20 eq) was added and the reaction was heated at 60 °C over a period of 16 h. The reaction was cooled to 0°C and sodium hydride (30 mg, 1.3 mmol, 5.4 eq) added. This was maintained at 0 °C for 1 h. Water (15 mL) was slowly added, and the aqueous layer was extracted with dichloromethane (3 x 15 mL). The organic layers were combined, washed with 20 mL of brine, dried over magnesium sulfate, the solvent was removed under reduced pressure. The residue was purified via preparatory HPLC (HPLC method: C18 ODS, 10-90% $CH_3CN/H_2O$ 0.1%TFA).

**C4. Example 10. Preparation of N-(6-chloro-4-{[4-(5,6-dihydro-1,4,2-dioxazin-3-yl)benzyl]amino}-2-quinazolinyl)-N-(2-thienylmethyl)amine.**

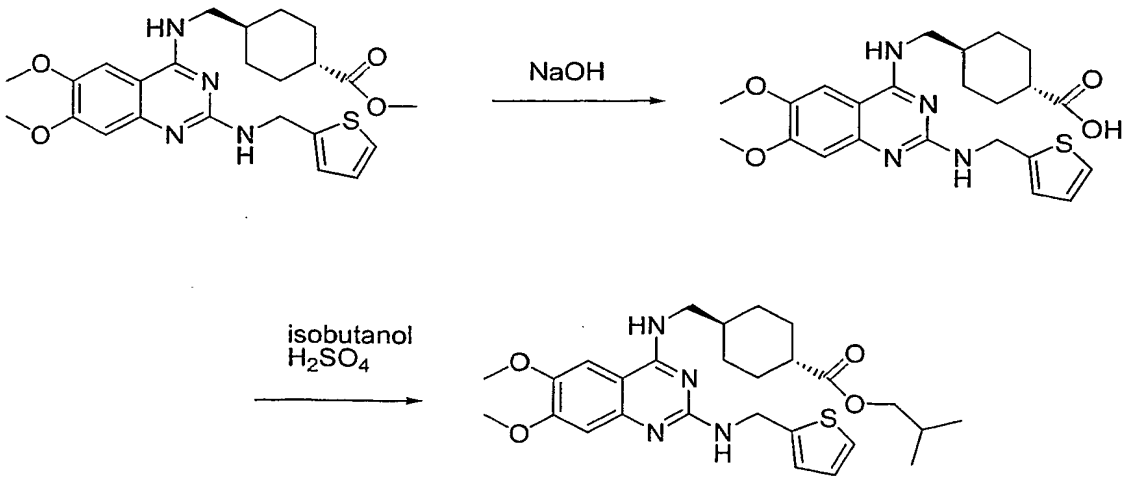



**Step 1.** 4-[({6-Chloro-2-[(2-thienylmethyl)amino]-4-quinazolinyl}amino)methyl]benzoic acid (1 eq) was dissolved in DMF (0.23 M) and cooled to –30 °C when

hydroxybenzatriazolehydrate (1.7 eq) and 1-[3-(dimethylaminopropyl)]-3-ethylcarbo diimide hydrochloride (1.7 eq) were added. This was allowed to stir for 15 min and 2-(aminooxy)ethanol (1.4 eq) in a solution of DMF (0.33 M was added via syringe. The reaction was gradually allowed to reach rt and was magnetically stirred over a period of 18 h. The reaction was dissolved in EtOAc and water and poured into a seperatory funnel. The layers were separated and the aqueous was extracted with EtOAc (3x). The combined organics were washed with 10% citric acid (2x), 10% $NaHCO_3$ (2x), satd. NaCl, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting crude solid 4-[({6-chloro-2-[(2-thienylmethyl)amino]-4-quinazolinyl}amino)methyl]-N-(2-hydroxy-ethoxy)benzamide was a 1:1 mixture of starting material and product and used without purification.

**Step 2.** 4-[({6-Chloro-2-[(2-thienylmethyl)amino]-4-quinazolinyl}amino)methyl]-N-(2-hydroxyethoxy)benzamide (1 eq) was dissolved in THF (0.02 M) were magnetically stirred as a suspension and the Burgess reagent (1.1 eq) was added in one portion. The reaction was heated at 80 °C over a period of 3 h. The reaction was cooled, concentrated and purified by flash silica column chromatography (1/1 EtOAc/Hex) to give N-(6-chloro-4-{[4-(5,6-dihydro-1,4,2-dioxazin-3-yl)benzyl]amino}-2-quinazolinyl)-N-(2-thienylmethyl)amine in 16% overall yield.

**C5. Example 11. Preparation of isobutyl 4-[({6,7-dimethoxy-2-[(2-thienylmethyl)amino]-4-quinazolinyl}amino)methyl]benzoate.**

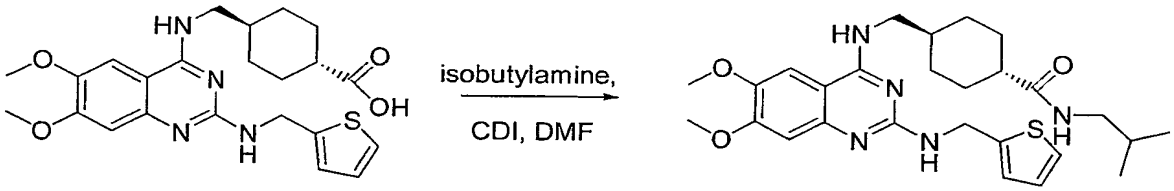



**Step 1:** To methyl 4-[({6,7-dimethoxy-2-[(2-thienylmethyl)amino]-4-quinazolinyl}amino)methyl]benzoate (0.51 g) in methanol (10 mL) was added 50% sodium hydroxide

(0.1 mL) and the reaction was heated to 65 °C for one hour, then stirred at rt for 16 h. The reaction was cooled and 1N hydrochloric acid was added until a pH=7 was achieved. Solids emerged and were filtered to give 200 mg of 4-[({6,7-dimethoxy-2-[(2-thienylmethyl)amino]-4-quinazolinyl}amino)methyl]benzoic acid (40%).

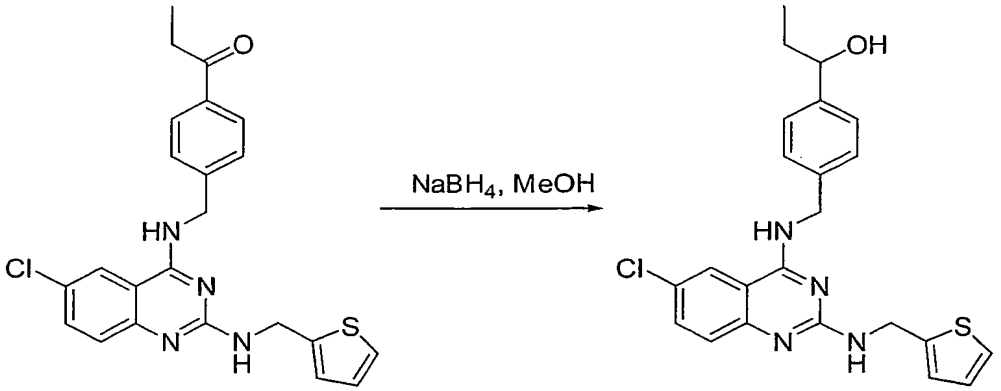
**Step 2:** To 4-[({6,7-dimethoxy-2-[(2-thienylmethyl)amino]-4-quinazolinyl} amino) methyl]benzoic acid (0.050 g) in *iso*-butanol (3 mL) was added a catalytic amount of conc. sulfuric acid and the reaction was heated to 100 °C for 2 h. It was cooled, taken up in ethyl acetate, washed with 1N hydrochloric acid, the organic layers were filtered, dried with magnesium sulfate, filtered, and concentrated to give 60 mg of *iso*-butyl 4-[({6,7-dimethoxy-2-[(2-thienylmethyl)amino]-4-quinazolinyl}amino)methyl]benzoate (99%).

**C6. Example 12. Preparation of 4-[({6,7-dimethoxy-2-[(2-thienylmethyl)amino]-4-quinazolinyl}amino)methyl]-N-isobutylbenzamide.**



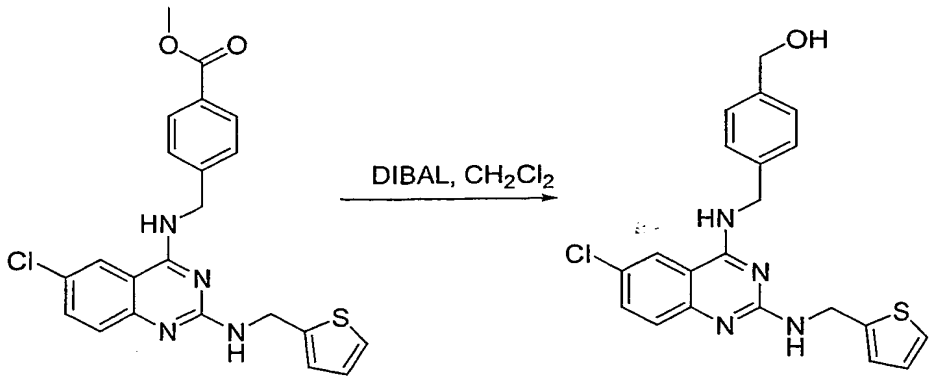

To 4-[({6,7-dimethoxy-2-[(2-thienylmethyl)amino]-4-quinazolinyl}amino)methyl] benzoic acid (0.100 g, 0.22 mmol, 1.0eq.) in DMF (10 mL) was added carboxydiimidazole (0.036 g, 0.22 mmol, 1eq.) and the reaction was heated to 60 °C for 1 h. Isobutylamine (0.32 g, 4.4 mmol., 20 eq.) was then added and the reaction continued to stir at 60 °C for 3 h. It was cooled, diluted with ethyl acetate, washed with water, dried with magnesium sulfate, filtered and the solvent was removed under reduced pressure. The crude oil was purified by flash chromatography (0-20% methanol/chloroform) to give 23 mg of 4-[({6,7-dimethoxy-2-[(2-thienylmethyl)amino]-4-quinazolinyl}amino) methyl]-N-isobutylbenzamide (21%).

**C7. Example 13. Preparation of 1-{4-[({6-chloro-2-[(2-thienylmethyl)amino]-4-quinazolinyl}amino)methyl]phenyl}-1-propanol.**




Sodium borohydride (0.005 g ,0.14 mmol, 1.5 eq.) was added to a solution of 1-{4-[({6-chloro-2-[(2-thienylmethyl)amino]-4-quinazolinyl}amino)methyl]phenyl}-1-propanone (0.040 g, 0.09 mmol, 1.0 eq) in ethyl alcohol (5 mL) and were magnetically stirred at rt over a period of 16 h. An aqueous solution of ammonium hydroxide (10%, 5 mL) was added and the ethyl alcohol was removed *in vacuo*. Methylene chloride (25 mL) was added and this solution was washed with deionized water (25 mL), dried over magnesium sulfate and then filtered. The solution was concentrated under reduced pressure, and purified by column chromatography (30-70% Ethyl acetate:Hexanes) to yield 15 mg of 1-{4-[({6-chloro-2-[(2-thienylmethyl)amino]-4-quinazolinyl}amino) methyl]phenyl}-1-propanol as a colorless solid (38%). LC/MS 439.3 (100%).

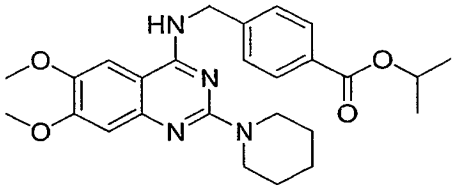
**C8. Example 14. Preparation of {4-[({6-chloro-2-[(2-thienylmethyl)amino]-4-quinazolinyl}amino)methyl]phenyl}methanol.**




Diisobutyl aluminum hydride (1M, in dichloromethane, 0.96 mL, 0.96 mmol, 3 eq) was added dropwise to a previously cooled (0 °C, via ice/water bath) suspension of methyl 4-

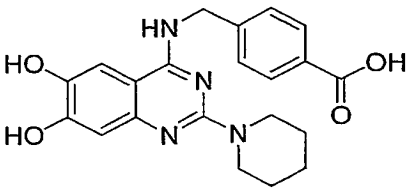
[({6-chloro-2-[(2-thienylmethyl)amino]-4-quinazolinyl}amino)methyl]benzoate (0.140 g, 0.32 mmol, 1.0 eq) in dichloromethane (2 mL), and were magnetically stirred at rt over a period of 16 h. An aqueous solution of Rochelle salt (50 mL) and methylene chloride (50 mL) was added and the organic layer was separated, dried over magnesium sulfate and then filtered. The solution was concentrated *in vacuo*, and purified by HPLC ($ACN/H_2O$) to give 1 mg of {4-[({6-chloro-2-[(2-thienylmethyl)amino]-4-quinazolinyl}amino) methyl]phenyl} methanol as a colorless solid (<1 %). $^1H$ NMR (MeOH, 300 MHz). LC/MS 439.3 (100%).

**C9. Example 15. Preparation of isopropyl 4-({[6,7-dimethoxy-2-(1-piperidinyl)-4-quinazolinyl]amino}methyl)benzoate**



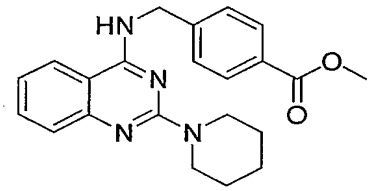
To a suspension of methyl 4-({[6,7-dimethoxy-2-(1-piperidinyl)-4-quinazolinyl] amino}methyl)benzoate (3.50 g, 8.02 mmol) in isopropanol (500 mL) in an oven dried flask under argon was added sodium isopropoxide solution (125 mL of 1.74 M solution, 2.17 mmol). The cloudy suspension was stirred at 35 °C for 16 h, after which time the reaction becomes clear, then concentrated at rt under reduced pressure to give a white solid. This was quenched by suspending it in 0.05M HCl (aq) (125 mL) with sonication to a final pH of 1.5. The white solid was filtered through a course frit and washed well with water (3 x 150 mL). The solid was dried under $P_2O_5$ *in vacuo* to give 3.70 g of isopropyl 4-({[6,7-dimethoxy-2-(1-piperidinyl)-4-quinazolinyl]amino}methyl)benzoate as a colorless solid in (99%). TLC: Rf = 0.64 (EtOAc); HPLC/MS: [M+H]+obs = 465 @ tr = 2.59 min. (ESI+).

**C10. Example 16. Preparation of 4-({[6,7-dihydroxy-2-(1-piperidinyl)-4-quinazolinyl] amino}methyl)benzoic acid.**



To a suspension of 4-({[6,7-dimethoxy-2-(1-piperidinyl)-4-quinazolinyl]amino}methyl) benzoic acid (30 mg, 0.071 mmol) in dry $CH_2Cl_2$ (10 mL) at –78 °C under argon was added $BBr_3$ (1.42 mL of a 1.0M solution in $CH_2Cl_2$) dropwise over 30 min. The reaction was warmd to rt over 30 min and stirred an additional 72 h at rt. The reaction was quenched with water (10 mL) and extracted with $CH_2Cl_2$. A brown solid which forms in the biphase was filtered off and washed with water (20 mL) and $CH_2Cl_2$ (20 mL) and dried *in vacuo* to give 3.0 mg of 4-({[6,7-dihydroxy-2-(1-piperidinyl)-4-quinazolinyl] amino}methyl)benzoic acid in (11%). TLC: Rf = 0.85 (25% MeOH/EtOAc); HPLC/MS: [M+H]+obs = 395 @ tr = 2.06 min. (ESI+).

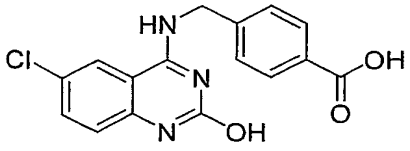
**C11. Example 17. Preparation of methyl 4-({[2-(1-piperidinyl)-4-quinazolinyl]amino} methyl)benzoate.**



To a solution of methyl 4-({[6-chloro-2-(1-piperidinyl)-4-quinazolinyl]amino}methyl) benzoate (50 mg, 0.12 mmol) in MeOH (15 mL) was added 10% Pd/C (50 mg) and the reaction hydrogenated at 1 atm (balloon) with vigorous stirring for 24 h. The Pd/C was filtered off and the filtrate concentrated under reduced pressure to give an oil which crystallized. The crude product was recrystallized from minimal $CH_2Cl_2$ with added hexane to give 38 mg of the pure methyl 4-({[2-(1-piperidinyl)-4-quinazolinyl]amino} methyl)benzoate as a colorless solid (83%). TLC: Rf = 0.07 (20% EtOAc/hexane); HPLC/MS: [M+H]+obs = 377 @ tr = 3.06 min. (ESI+).

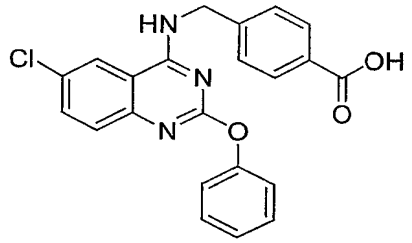
***D. Alternative Linkers or Cores***

**D1. Example 18. Preparation of 4-{[(6-chloro-2-hydroxy-4-quinazolinyl)amino] methyl} benzoic acid.**



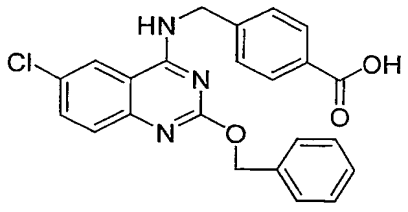
To a solution of 4-{[(2,6-dichloro-4-quinazolinyl)amino]methyl}benzoic acid (100 mg, 0.28 mmol) in dry 1,4-dioxane (30 mL) was added 5 M NaOH (aq) (11.04 mL, 55.22 mmol). The biphase was refluxed vigorously for 24 h. The reaction was quenched by addition of 2 M HCl (aq) (27 mL) and the cloudy mixture further diluted with Na/K tartrate/$NaHSO_4$ buffer at pH 6 (150 mL). This was extracted with EtOAc (2 x 400 mL) and the organic dried ($MgSO_4$) and concentrated *in vacuo* to give a crude yellow oil. Purification by silica gel chromatography (20-35% MeOH/EtOAc) afforded the product in 50% purity as a white solid. The semi-crude product was suspended in MeOH (1 mL) and sonicated for 5 min. Filtration and washing the white solid with MeOH (2 mL) gave 2 mg of the 4-{[(6-chloro-2-hydroxy-4-quinazolinyl)amino]methyl}benzoic acid (2%). TLC: Rf = 0.33 (25% MeOH/CH2Cl2); HPLC/MS: [M+H]+obs = 330 @ tr = 3.01 min. (ESI+).

**D2. Example 19. Preparation of 4-{[(6-chloro-2-phenoxy-4-quinazolinyl)amino] methyl} benzoic acid.**



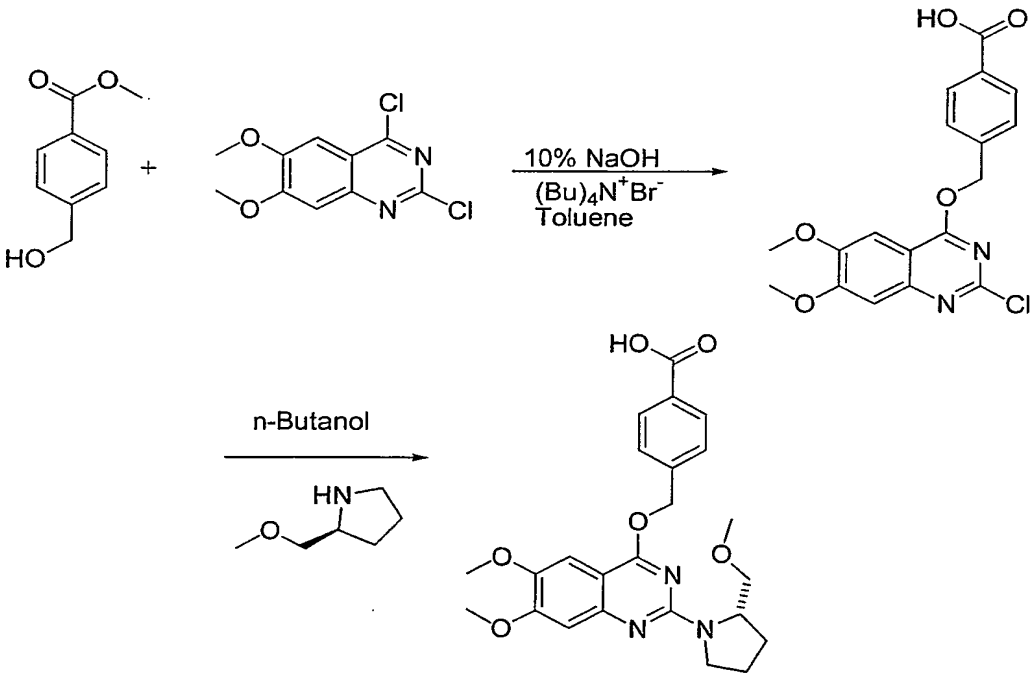

A mixture of 4-{[(2,6-dichloro-4-quinazolinyl)amino]methyl}benzoic acid (100 mg, 0.29 mmol) and phenol (270 mg, 2.87 mmol) was heated at 125 °C for 3 h, after which the slurry has become a clear yellow oil. The crude reaction was purified directly by silica gel chromatography (100% EtOAc → 25% MeOH/EtOAc) to give 4-{[(6-chloro-2-phenoxy-4-quinazolinyl)amino]methyl} benzoic acid as a white solid. TLC: Rf = 0.35 (25% MeOH/EtOAc); HPLC/MS: [M+H]+obs = 406 @ tr = 2.98 min. (ESI+).

**D3. Example 20. Preparation of 4-({[2-(benzyloxy)-6-chloro-4-quinazolinyl]amino} methyl)benzoic acid.**



To a suspension of 4-{[(2,6-dichloro-4-quinazolinyl)amino]methyl}benzoic acid (100 mg, 0.29 mmol) and benzyl alcohol (310 mg, 2.87 mmol) was added DBU (437 mg, 2.87 mmol). The clear yellow solution was stirred at 125 °C for 24 h. The reaction was quenched with 1M HCl (aq) to a final pH of 6. This was further diluted with water (75 mL) and extracted with EtOAc (2 x 150 mL). The organics were dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product as a gum. Purification by silica gel chromatography (100% EtOAc → 25% MeOH/EtOAc) afforded 13 mg of 4-({[2-(benzyloxy)-6-chloro-4-quinazolinyl]amino} methyl)benzoic acid as a colorless solid (11%). TLC: Rf = 0.40 (25% MeOH/EtOAc); HPLC/MS: [M+H]+obs = 420 @ tr = 2.29 min. (ESI+).

**D4. Example 21. Preparation of 4-[({6,7-dimethoxy-2-[(2S)-2-(methoxymethyl)-1-pyrrolidinyl]-4-quinazolinyl}oxy)methyl]benzoic acid.**

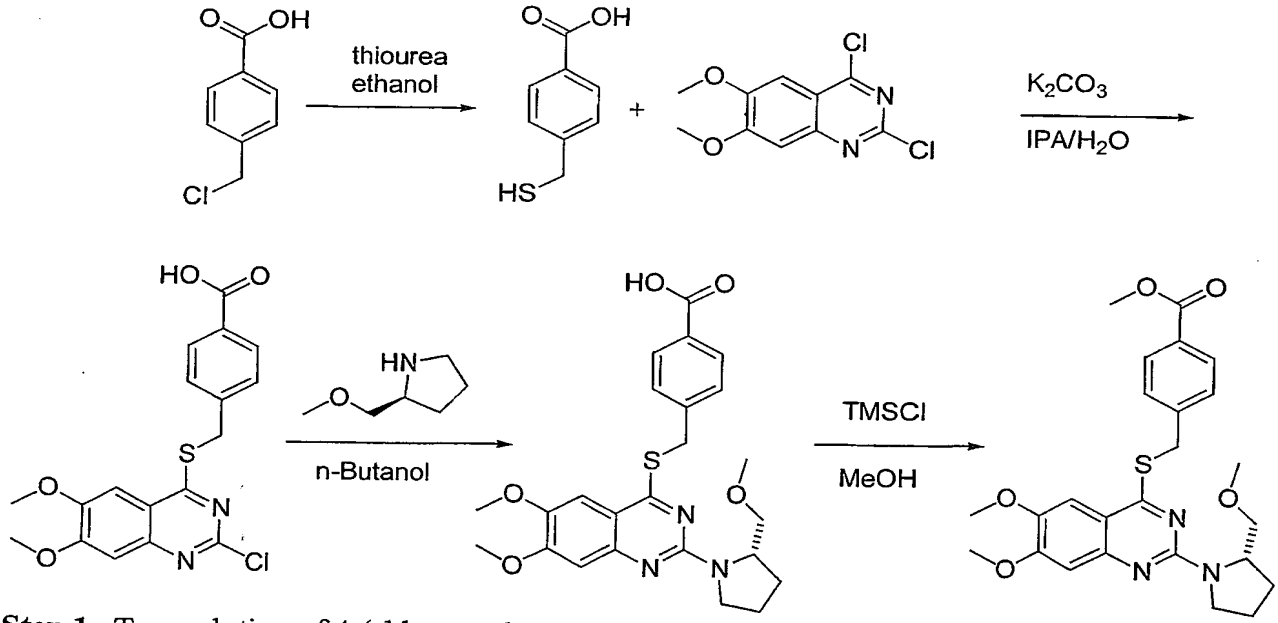



**Step 1.** To a solution of 2,4-dichloro-6,7-dimethoxyquinazoline (0.500 g, 1.93 mmol), tetrabutylammonium bromide (0.0311 g, 0.10 mmol), and 10% aqueous NaOH (4.0 mL) in toluene (4.8 mL) was added methyl 4-(hydroxymethyl)benzoate (0.330 g, 1.99 mmol) as a solution in toluene (3.3 mL), dropwise. The reaction was allowed to stir at rt for 18 h. Water (100 mL) was added and the mixture was extracted with EtOAc (3 x 100 mL). The combined organics were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford 112 mg of methyl 4-{[(2-chloro-6,7-dimethoxy-4-quinazolinyl)oxy]methyl}benzoate

(15%); $^1$H NMR (DMSO-$d_6$) 7.97 (d, $J$ = 7.3 Hz, 2H), 7.65 (d, $J$ = 7.3 Hz, 2H), 7.32 (d, $J$ = 7.4 Hz, 2H), 5.68 (s, 2H), 3.93 (s, 3H), 3.89 (s, 3H); ES MS $(M+H)^+$ = 375.2.

**Step 2.** A solution of (2S)-2-(methoxymethyl)pyrrolidine (0.033 g, 0.29 mmol) and 4-{[(2-chloro-6,7-dimethoxy-4-quinazolinyl)oxy]methyl}benzoic acid (0.108 g, 0.29 mmol) in *n*-butanol (1.5 mL) was heated at reflux for 18 h. The reaction was cooled to rt and the *n*-butanol was removed under reduced pressure. The residue was triturated with MeOH and filtered. The filtrate was concentrated under reduced pressure. The crude product was purified by preparative HPLC ($C_{18}$ ODS, 10-90% $CH_3CN/H_2O$ 0.1% TFA) to afford 3 mg of 4-[({6,7-dimethoxy-2-[(2S)-2-(methoxymethyl)-1-pyrrolidinyl]-4-quinazolinyl}oxy)methyl ]benzoic acid (2%); $^1$H NMR (MeOH-$d_4$) 8.03 (d, $J$ = 7.1 Hz, 2H), 7.55 (d, $J$ = 6.7 Hz, 2H), 7.34 (s, 1H), 7.05 (s, 1H), 5.69 (q, $J$ = 13.6 Hz, 2H), 4.37-4.30 (m, 1H), 3.94 (s, 3H), 3.88 (s, 3H), 3.68-3.60 (m, 1H), 3.58-3.51 (m, 2H), 2.15-1.91 (m, 4H), 1.28 (s, 1H); ES MS $(M+H)^+$ = 454.3; TLC ($CH_2Cl_2$/MeOH, 95:5): $R_f$ = 0.21.

**D5. Example 22. Preparation of methyl 4-[({6,7-dimethoxy-2-[(2S)-2-(methoxymethyl)-1-pyrrolidinyl]-4-quinazolinyl}sulfanyl)methyl] benzoate.**




**Step 1.** To a solution of 4-(chloromethyl)benzoic acid (1.00 g, 5.86 mmol) in EtOH (15 mL) was added thiourea (0.50 g, 5.86 mmol) as a solution in EtOH (5 mL), dropwise. The reaction was allowed to stir at room temperature overnight. Additional thiourea was added (0.23 g, 2.93 mmol) and the reaction was heated at reflux for 2 h, then allowed to cool to rt.

Water (30 mL) was added and the mixtue was made basic with the addition of 10% aqueous NaOH. The mixture was heated at reflux for 2 h. The reaction was cooled to rt and was washed with EtOAc (3 x 50 mL). 1N HCl was added to the aqueous portion to adjust the pH to 6 and the mixture was extracted with EtOAc (3 x 50 mL). The combined organics were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford 0.85 g of 4-(sulfanylmethyl)benzoic acid (86%); $^1$H NMR (DMSO-$d_6$) 12.87 (s, 1H), 7.86 (d, $J$ = 7.4 Hz, 2H), 7.43 (d, $J$ = 7.2 Hz, 2H), 3.77 (d, $J$ = 7.9 Hz, 2H), 2.96 (t, $J$ = 8.1 Hz, 1H); ES MS $(M+H)^+$= 169.0.

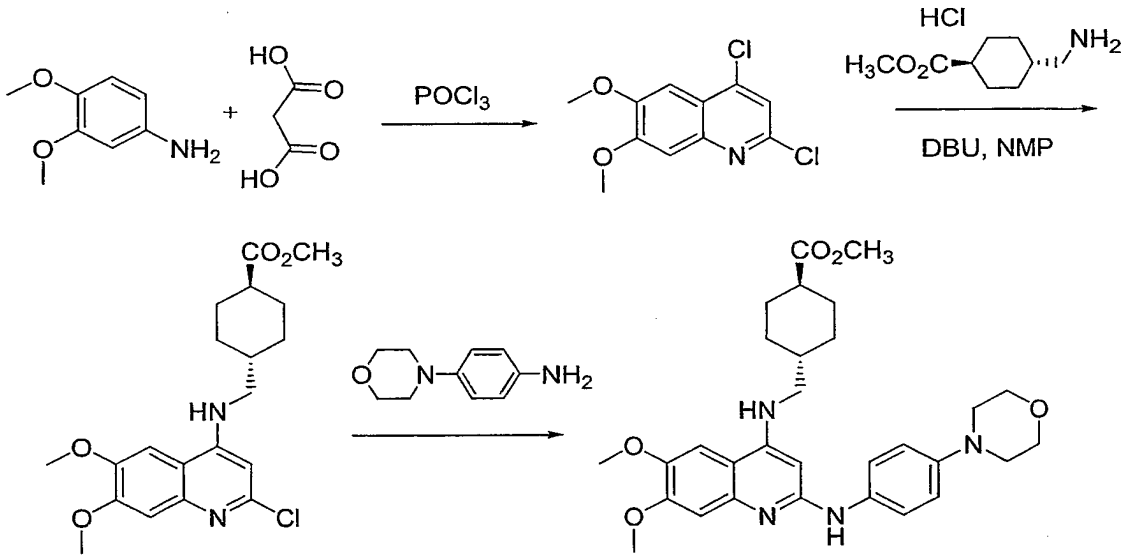
**Step 2.** A mixture of 2,4-dichloro-6,7-dimethoxyquinazoline (0.50 g, 1.93 mmol), 4-(sulfanylmethyl)benzoic acid (0.487 g, 2.89 mmol), and potassium carbonate (0.800 g, 5.79 mmol) in IPA/water (10 mL/5 mL) was heated at 60 °C overnight. The reaction was cooled to rt and 1N HCl was added to adjust the pH to 6. The resulting solid was collected by filtration and dried *in vacuo* at 45 °C overnight to afford 0.75 g of 4-{[(2-chloro-6,7-dimethoxy-4-quinazolinyl)sulfanyl]methyl}benzoic acid (99%); $^1$H NMR (DMSO-$d_6$) 12.92 (s, 1H), 7.89 (d, $J$ = 7.9 Hz, 2H), 7.61 (d, $J$ = 8.5 Hz, 2H), 7.29 (s, 1H), 7.13 (s, 1H), 4.66 (s, 2H), 3.94 (s, 3H), 3.91 (s, 3H); ES MS $(M+H)^+$= 391.2.

**Step 3.** A solution of (2S)-2-(methoxymethyl)pyrrolidine (0.06 g, 0.51 mmol) and 4-{[(2-chloro-6,7-dimethoxy-4-quinazolinyl)sulfanyl]methyl}benzoic acid (0.20 g, 0.51 mmol) in *n*-butanol (12 mL) was heated at reflux for 18 h. The reaction was cooled to rt and the *n*-butanol was removed *in vacuo*. The residue was taken up in MeOH and adhered to silica gel. The crude product was purified first by column chromatography (0-10% MeOH/$CH_2Cl_2$), followed by preparative HPLC ($C_{18}$ ODS, 10-90% $CH_3CN/H_2O$ 0.1% TFA) to afford 16 mg of 4-[({6,7-dimethoxy-2-[(2S)-2-(methoxymethyl)-1-pyrrolidinyl]-4-quinazolinyl}sulfanyl)methyl] benzoic acid (7%); $^1$H NMR (Acetone-$d_6$) 8.01 (d, $J$ = 6.1 Hz, 2H), 7.78-7.63 (m, 3H), 7.26 (s, 1H), 4.84 (s, 2H), 4.72 (s, 1H), 3.99 (s, 3H), 3.96 (s, 3H), 3.39-3.34 (m, 2H), 2.74 (s, 3H), 2.23-2.18 (m, 4H), 1.99-1.95 (m, 2H); ES MS $(M+H)^+$= 470.4; TLC ($CH_2Cl_2$/MeOH, 90:10): $R_f$ = 0.60.

**Step 4.** A solution of 4-[({6,7-dimethoxy-2-[(2S)-2-(methoxymethyl)-1-pyrrolidinyl]-4-quinazolinyl}sulfanyl)methyl] benzoic acid (0.025 g, 0.05 mmol) and chlorotrimethylsilane (0.011 g, 0.10 mmol) in MeOH (1.0 mL) was stirred rt for 18 h. Additional

chlorotrimethylsilane (0.113 g, 0.10 mmol) was added and the mixture was allowed to stir 24 h. The mixture was concentrated under reduced pressure. The residue was taken up in MeOH and, again, concentrated under reduced pressure. The dilution and concentration was repeated 4 times. The crude product was purified by preparative TLC (95:5 $CH_2Cl_2$/MeOH) and dried *in vacuo* to afford 25 mg of methyl 4-[({6,7-dimethoxy-2-[(2S)-2-(methoxymethyl)-1-pyrrolidinyl]-4-quinazolinyl}sulfanyl)methyl] benzoate (97%); mp = 90-95 °C; ES MS $(M+H)^+$=484.2; TLC (50:50 Hexanes/EtOAc): $R_f$=0.36.

**D6. Example 23. Preparation of methyl 4-{[(6,7-dimethoxy-2-{[4-(4-morpholinyl)phenyl]amino}-4-quinolinyl)amino]methyl} cyclohexane carboxylate.**




**Step 1.** To a heterogeneous magnetically stirred solution of malonic acid (5.4 g, 52 mmol, 1.0 eq) in phosphorous oxychloride (60, 390 mmol, 7.5 eq) was added 3,4-dimethoxyaniline (10 g, 65 mmol, 1.25 eq). The reaction heated to reflux at 115 °C for 2 h when it was cooled to rt and carefully added to 500 mL ice. The resulting aqueous layer was extracted with dichloromethane (2 x 300 mL). The organic layers were combined, washed with brine (1 x 300 mL), dried over magnesium sulfate and concentrated *in vacuo* to yield 6 g of 2,4-dichloro-6,7-dimethoxyquinoline (45%).

**Step 2.** A solution of 2,4-dichloro-6,7-dimethoxyquinoline (3g, 11.7 mmol, 1 eq), methyl 4-(aminomethyl)cyclohexanecarboxylate (9.7 g, 46.8 mmol, 4 eq), DBU (7 mL, 46.8 mmol, 4 eq) in 60 mL of NMP was magnetically stirred at 120 °C in a sealed tube over a period of 16 h. The reaction was concentrated *in vacuo* and the resulting residue diluted with 100 mL of

dichloromethane. The organic layer was washed with water(6 x 75 mL) and then brine (2 x 75 mL), dried over magnesium sulfate, and concentrated *in vacuo*. Flash chromatography (50:50 EtOAc:Hex) gave methyl 4-{[(2-chloro-6,7-dimethoxy-4-quinolinyl)amino]methyl}cyclohexanecarboxylate as a yellow oil, which was diluted with 50 mL dichloromethane. The organic layer was washed with water (6 x 50 mL) and then brine (2 x 50 mL), dried over magnesium sulfate, and concentrated *in vacuo* to give 2.1 g of methyl 4-{[(2-chloro-6,7-dimethoxy-4-quinolinyl)amino]methyl}cyclohexane carboxylate as a off-white solid (46%).

**Step 3.** 4-(4-Morpholinyl)phenylamine (0.89 g, 5 mmol, 20 eq) and methyl 4-{[(2-chloro-6,7-dimethoxy-4-quinolinyl)amino]methyl}cyclohexanecarboxylate (100 mg, 0.25 mmol, 1 eq) were magnetically stirred at 140 °C in a sealed tube over a period of 16 h. Preparatory HPLC[1] yielded 4 mg of pure methyl 4-{[(6,7-dimethoxy-2-{[4-(4-morpholinyl)phenyl]amino}-4-quinolinyl)amino]methyl} cyclohexanecarboxylate. (3%). **$^1$H NMR** (Methanol-$d_4$) 7.54 (s, 1H), 7.25 (d, $J$ = 9Hz, 2H), 7.13 (s, 1H), 7.10 (d, $J$ = 9Hz, 2H), 5.74 (s, 1H), 3.94 (s, 3H), 3.93 (s, 3H), 3.86 (t, $J$ = 4.9Hz, 4H), 3.65 (s, 3H), 3.20-3.16 (m, 6 H), 2.38-2.28 (m, 1H), 2.05-2.00 (m, 2H), 1.91-1.82 (m, 2H), 1.78-1.66 (m, 1H), 1.49-1.34 (m, 2H), 1.16-1.0 (m, 2H); **LC-MS** (ES) 535.6 $(M+H)^+$; **TLC** (5:95 $MeOH/CH_2Cl_2$) Rf = 0.17.

Examples 24 - 345 listed in the tables below were synthesized by the preparative methods described above or by using other known synthetic techniques such as those described by D. J. Brown, *Fused Pyrimidines (part 1. - Quinazolines)*, by W. L. F. Amarego, publ. by New York Interscience, (1967); D. J. Brown, *Quinazolines (Supplement I)*, publ. by John Wiley & Sons, (1996); Vol. 32, *Quinolines (Part I)*, edited by Gurnos Jones, Interscience (a division of John Wiley & Sons), (1977), (Part II - 1982), (Part III - 1990), each of which is incorporated in its entirety by reference (Each of the references are part of the Monograph series entitled "The Chemistry of Heterocyclic Compounds", Monograph editors: Weissberger and Taylor).

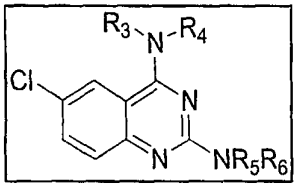
Table 1 shows Examples 24 - 237 which are various embodiments of the described compounds wherein $R_2$ = Cl.

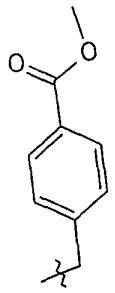
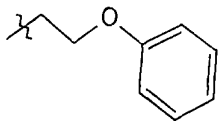
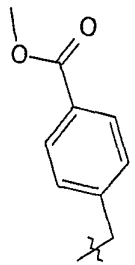
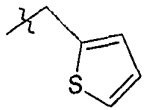
Table 2 shows Examples 238 - 307 which are various embodiments of the described compounds when $R_1 = R_2 = -OCH_3$.

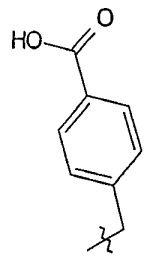
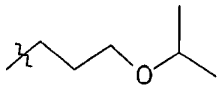
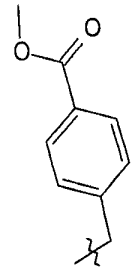
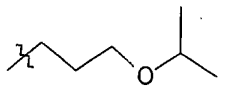
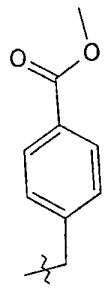
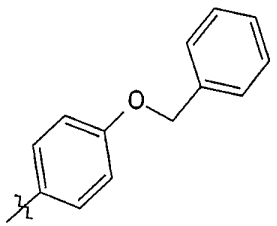
Table 3 shows Examples 308 - 346 which are various other embodiments of the described invention.

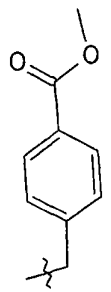
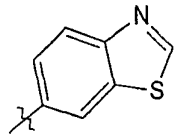
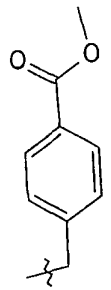
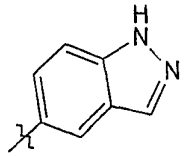
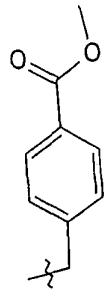
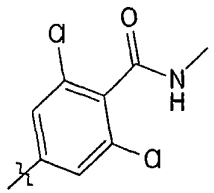
Table 4 shows the accompanying analytical data for Examples 308 - 346 from Table 3.

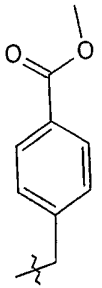
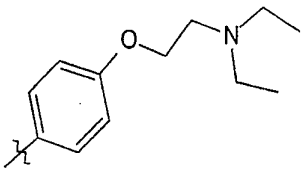
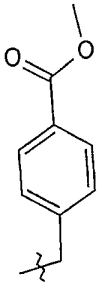
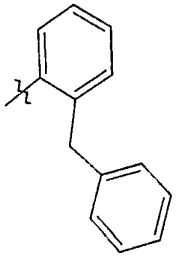
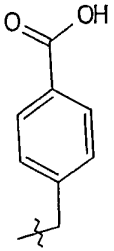
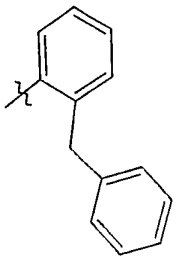
**Table 1. 6-Chloroquinazolines**

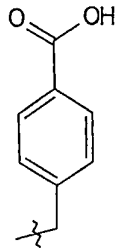
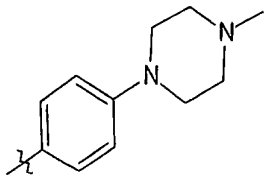
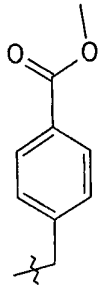
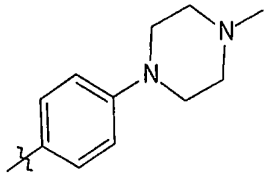
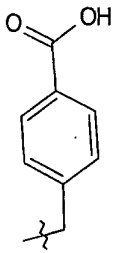
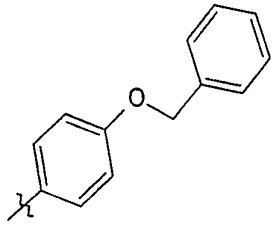


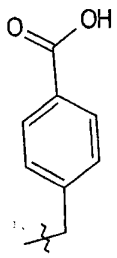
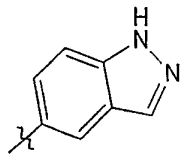
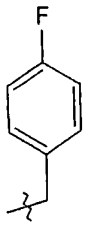
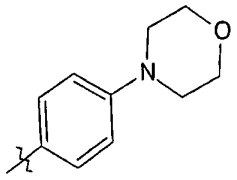
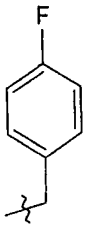
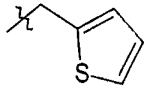

| Ex. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp (°C) | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 24 | H |  |  | H | TLC Rf = 0.19 (3/2 Hex/EtOAc) | 463 | | A6, B1 |
| 25 | H |  |  | H | TLC Rf = 0.33 (3/2 Hex/EtOAc) | 439 | | A6, B1 |

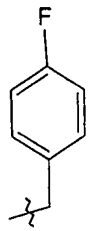
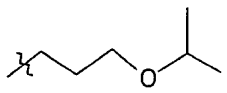
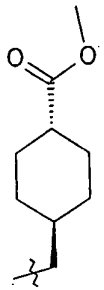
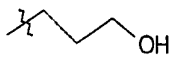
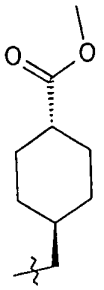
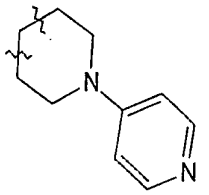
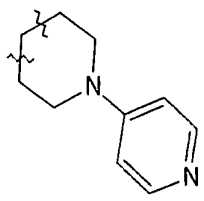
| Ex. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp (°C) | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 26 | H |  |  | H | TLC Rf = 0.23 (9/1 CH2Cl2/MeOH) | 429 | | A6, B1, C1 |
| 27 | H |  |  | H | TLC Rf = 0.13 (3/2 Hex/EtOAc) | 443 | | A6, B1 |
| 28 | H |  |  | H | HPLC RT= 2.88 (98%H20-98%CH3CN) | 525 | | A6, B1 |

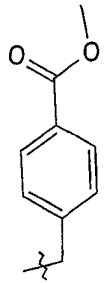
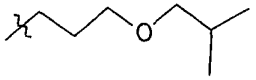
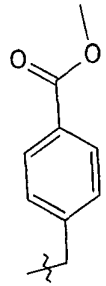
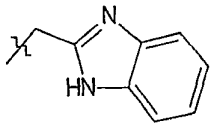
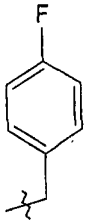
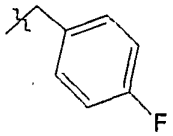
| Ex. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp (°C) | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 29 | H |  |  | H | HPLC RT=2.40 (98%H20-98%CH3CN) | 476 | | A6, B1 |
| 30 | H |  |  | H | HPLC RT = 2.27 (98%H20-98%CH3CN) | 459 | | A6, B1 |
| 31 | H |  |  | H | HPLC RT = 2.36 (98%H20-98%CH3CN) | 546 | | A6, B1 |

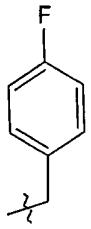
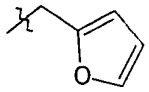
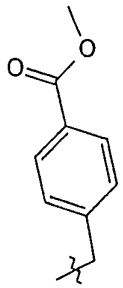
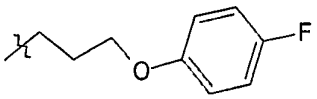
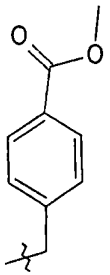
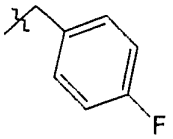
| Ex. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp (°C) | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 32 | H |  |  | H | HPLC RT=2.09 (98%H2O-98%CH3CN) | 534 | | A6, A10, B1 |
| 33 | H |  |  | H | HPLC RT=2.75 (98%H20-98%HCN) | 509 | | A6, B1 |
| 34 | H |  |  | H | HPLC RT = 2.49 (98%H20-98%CH3CN) | 495 | | A6, B1, C1 |

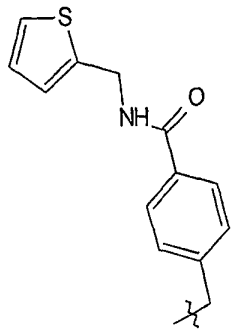
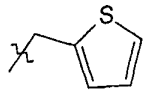
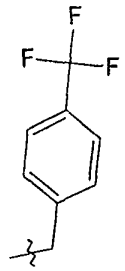
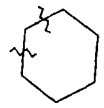
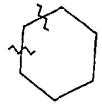
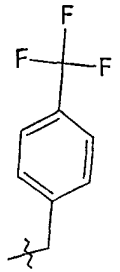
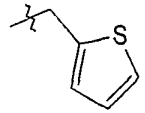
| Ex. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp (°C) | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 35 | H |  |  | H | HPLC RT = 1.76 (98%H2O-98%CH3CN) | 503 | | A6, B1 |
| 36 | H |  |  | H | HPLC RT=2.02 (98%H20-98%CH3CN) | 517 | | A6, B1, C1 |
| 37 | H |  |  | H | HPLC RT =2.62(98%H2O-98%CH3CN) | 511 | | A6, B1, C1 |

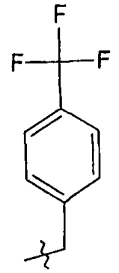
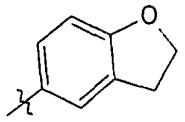
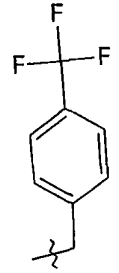
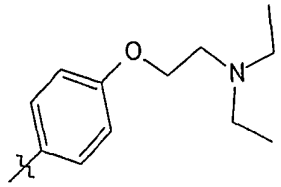
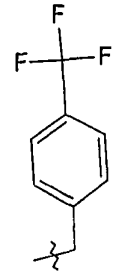
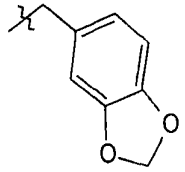
| Ex. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp (°C) | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 38 | H |  |  | H | HPLC RT=2.02(98%H2O-98%CH3CN) | 445 | | A6, B1, C1 |
| 39 | H |  |  | H | HPLC RT=2.47 (98%H2O-98%CH3CN) | 464 | | A6, B1 |
| 40 | H |  |  | H | HPLC RT=2.55 (98%H2O-98%CH3CN) | 399 | | A6, B1 |

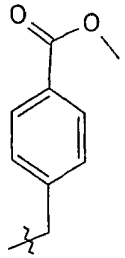
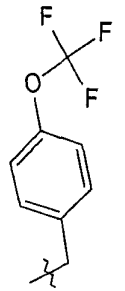
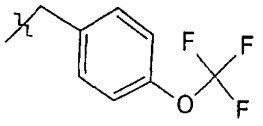
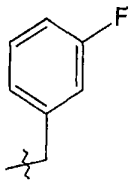
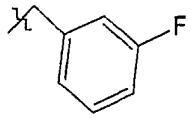
| Ex. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp (°C) | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 41 | H |  |  | H | HPLC RT=2.67 (98%H2O-98%CH3CN) | 403 | | A6, B1 |
| 42 | H |  |  | H | HPLC RT=2.14 (98%H2O-98%CH3CN) | 407 | | A6, B1 |
| 43 | H |  |  |  | TLC Rf = 0.58 (9/1 CH2Cl2/MeOH) | 495 | | A6, B1 |

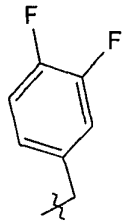
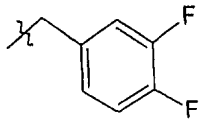
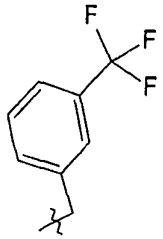
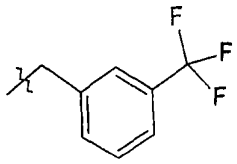
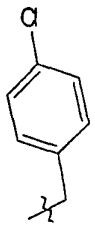
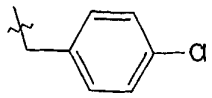
| Ex. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp (°C) | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 44 | H |  |  | H | TLC Rf = 0.22 (3/2 Hex/EtOAc) | 457 | | A6, B1 |
| 45 | H |  |  | H | HPLC RT=1.62 (98%H2O-98%CH3CN) | 473 | | A6, B1 |
| 46 | H |  |  | H | TLC Rf = 0.12 (3/2 Hex/EtOAc) | 411 | | A6, B1 |

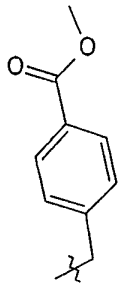
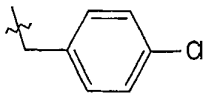
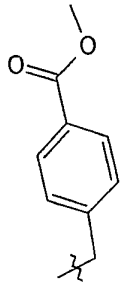
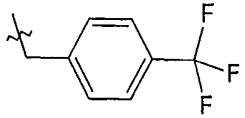
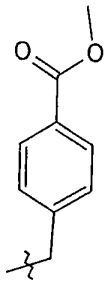
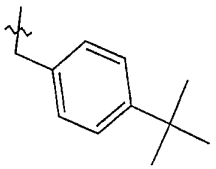
| Ex. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp (°C) | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 47 | H |  |  | H | TLC Rf = 0.27 (3/2 Hex/EtOAc) | 383 | | A6, B1 |
| 48 | H |  |  | H | HPLC RT=2.67 (10-90% CH3CN-H20) | 495 | | A6, A9, B1 |
| 49 | H |  |  | H | | 451 | | A6, B1 |

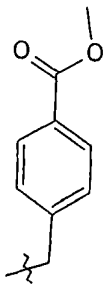
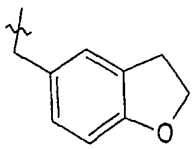
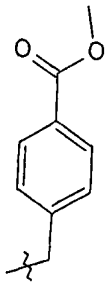
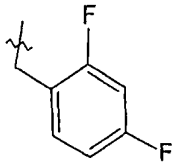
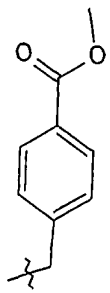
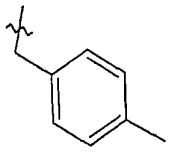
| Ex. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp (°C) | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 50 | H |  |  | H | TLC Rf = 0.56 (95/5 CH2Cl2/MeOH) | 520 | | A6, B1, C1, C2 |
| 51 | H |  |  |  | TLC Rf = 0.55 (95/5 CH2Cl2/MeOH) | 421 | | A6, B1 |
| 52 | H |  |  |  | TLC Rf = 0.78 (95/5 CH2Cl2/MeOH) | 463 | | A6, B1 |

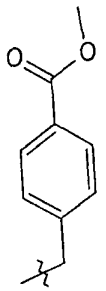
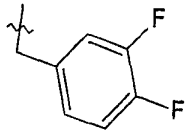
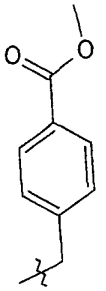
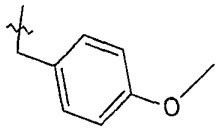
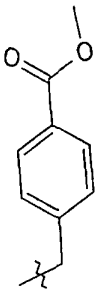
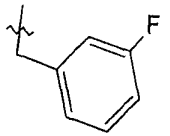
| Ex. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp (°C) | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 53 | H |  |  | H | TLC Rf = 0.20 (3/2 Hex/EtOAc) | 471 | | A6, B1 |
| 54 | H |  |  | H | HPLC RT = 2.24 (10-90%CH3CN/H2O) | 544 | | A6, A10, B1 |
| 55 | H |  |  | H | HPLC RT=2.72 (10-90% CH3CN/H2O) | 487 | | A6, B1 |

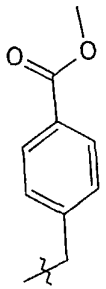
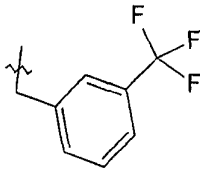
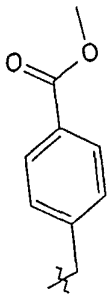
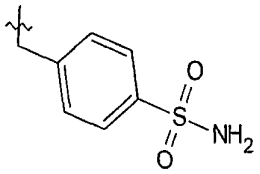
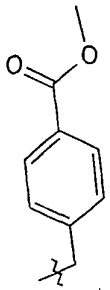
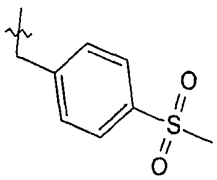
| Ex. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp (°C) | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 56 | H |  |  |  | TLC (75% Hex/25%EtOAc) Rf = 0.45 | 397.4 | >225 | A6, B1 |
| 57 | H |  |  | H | TLC (80% EtOAc/20% MeOH) Rf = 0.89 | 543.1 | >225 | A6, B1 |
| 58 | H |  |  | H | TLC (90% EtOAc/10% MeOH) Rf = 0.87 | 411.5 | >210 | A6, B1 |

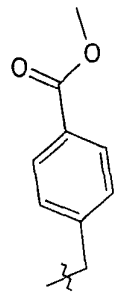
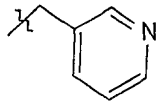
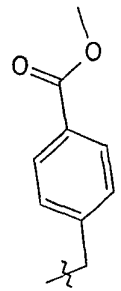
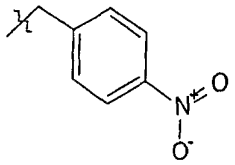
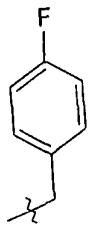
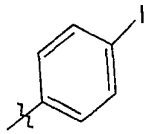
| Ex. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp (°C) | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 59 | H |  |  | H | TLC ( 1/9 MeOH/EtOAc) Rf = 0.85 | 447.5 | 169-170 | A6, B1 |
| 60 | H |  |  | H | TLC (1/9 MeOH/EtOAc) Rf = 0.92 | 511.5 | 144-145 | A6, B1 |
| 61 | H |  |  | H | TLC (1/9 MeOH/EtOAc) Rf = 0.82 | 443.6 | 155 | A6, B1 |

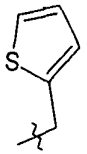
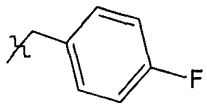
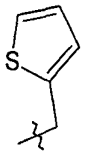
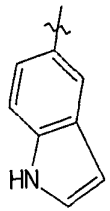
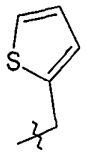
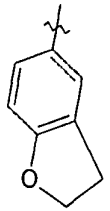
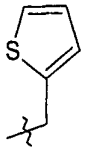
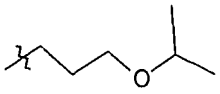
| Ex. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp (°C) | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 62 | H |  |  | H | TLC (EtOAc) Rf = 0.78 | 467.3 | >210 | A6, B1 |
| 63 | H |  |  | H | TLC (EtOAc) Rf = 0.80 | 501.3 | >210 | A6, B1 |
| 64 | H |  |  | H | TLC (EtOAc) Rf = 0.77 | 489.4 | 200-202 | A6, B1 |

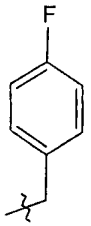
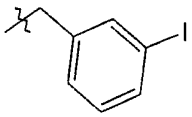
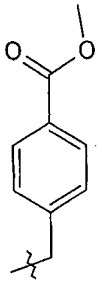
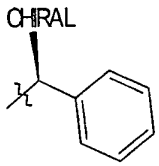
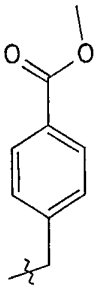
| Ex. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp (°C) | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 65 | H |  |  | H | TLC (EtOAc) Rf = 0.75 | 475.3 | 194-196 | A6, B1 |
| 66 | H |  |  | H | TLC (EtOAc) Rf = 0.85 | 469.3 | 188-189 | A6, B1 |
| 67 | H |  |  | H | TLC (EtOAc) Rf = 0.72 | 447.3 | >210 | A6, B1 |

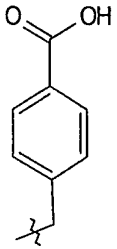
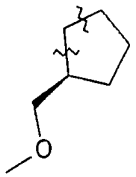
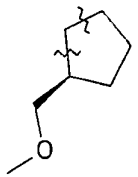
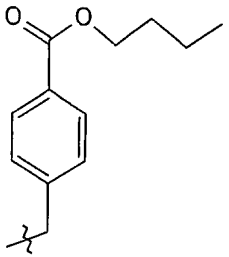
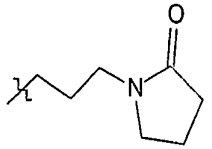
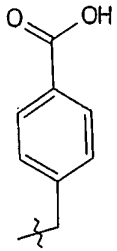
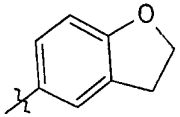
| Ex. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp (°C) | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 68 | H |  |  | H | TLC (EtOAc) Rf = 0.83 | 469.5 | 200-201 | A6, B1 |
| 69 | H |  |  | H | TLC (EtOAc) Rf = 0.73 | 463.5 | 191-193 | A6, B1 |
| 70 | H |  |  | H | TLC (EtOAc) Rf = 0.83 | 451.5 | 190-192 | A6, B1 |

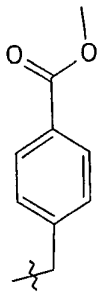
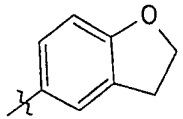
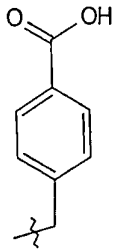
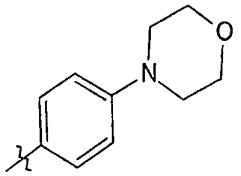
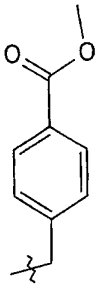
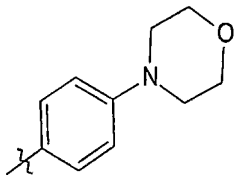
| Ex. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp (°C) | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 71 | H |  |  | H | TLC (EtOAc) O.89 | 501.5 | 191-193 | A6, B1 |
| 72 | H |  |  | H | TLC (EtOAc) Rf = 0.73 | 512.6 | >210 | A6, B1 |
| 73 | H |  |  | H | TLC (EtOAc) Rf = 0.75 | 511.2 | >210 | A6, B1 |

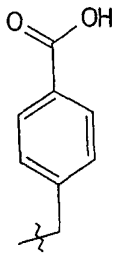
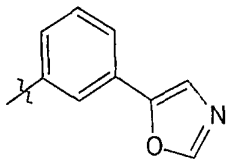
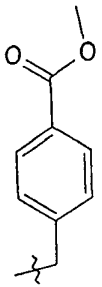
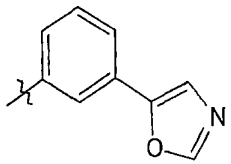
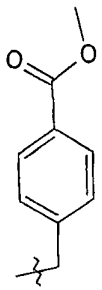
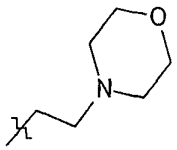
| Ex. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp (°C) | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 74 | H |  |  | H | TLC (9/1 EtOAc/MeOH) Rf = 0.73 | 434.4 | 100-105 | A6, B1 |
| 75 | H |  |  | H | TLC (EtOAc) Rf = 0.60 | 478.4 | 207-209 | A6, B1 |
| 76 | H |  |  | H | TLC (1/4 EtOAc/Hex) Rf = 0.60 | 505.2 | 185-185.5 | A6, B1 |

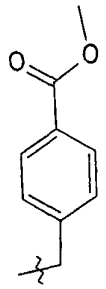
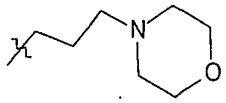
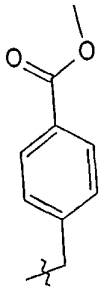
| Ex. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp (°C) | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 77 | H |  |  | H | TLC (1/1 Hex/ EtOAc) Rf = 0.76 | 399.6 | 139.5-140 | A6, B1 |
| 78 | H |  |  | H | TLC (1/1 EtOAc/Hex) Rf = 0.57 | 406.5 | 201-203 | A6, B1 |
| 79 | H |  |  | H | TLC (1/1 EtOAc/Hex) Rf = 0.73 | 409.2 | 171-173 | A6, B1 |
| 80 | H |  |  | H | TLC (1/1 EtOAc/Hex) Rf = 0.60 | 391.3 | 94-95 | A6, B1 |

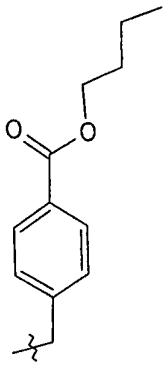
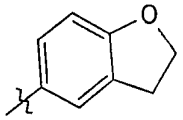
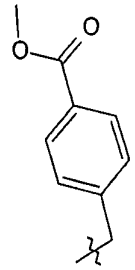
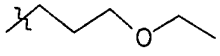
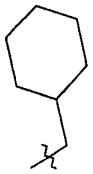
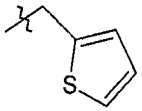
| Ex. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp (°C) | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 81 | H |  |  | H | TLC (1/1 Hex/EtOAc) Rf = 0.64 | 519.2 | 150-151 | A6, B1 |
| 82 | H |  |  | H | TLC (1/1 Hex/EtOAc) Rf = 0.54 | 447.3 | 88-90 | A6, B1 |
| 83 | H |  |  | H | TLC (1/1 Hex/EtOAc) Rf = 0.54 | 447.3 | 88-90 | A6, B1 |

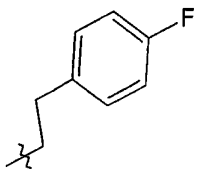
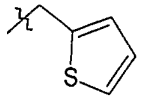
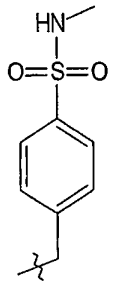
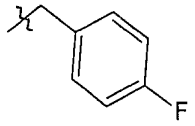
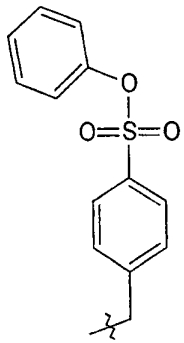
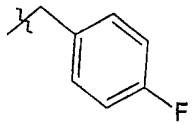
| Ex. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp (°C) | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 84 | H |  |  |  | | | | A6, B1, C1 |
| 85 | H |  |  | H | TLC Rf = 0.16 (9/1 CH2Cl2/MeOH) | M+H 510.5 | | A6, B1, C1, C3 |
| 86 | H |  |  | H | TLC Rf = 0.17 (9/1 CH2Cl2/MeOH) | M+H 447 | | A6, B1, C1 |

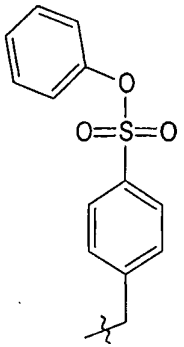
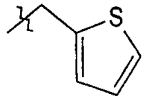
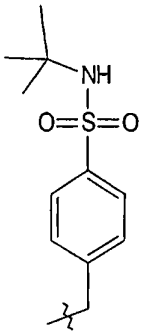
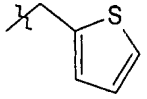
| Ex. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp (°C) | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 87 | H |  |  | H | TLC Rf = 0.47 (1/1 Hex/EtOAc) | M+H 461 | | A6, B1 |
| 88 | H |  |  | H | TLC Rf = 0.15 (9/1 CH2Cl2/MeOH) | M+H 490 | | A6, B1, C1 |
| 89 | H |  |  | H | TLC Rf = 0.10 (1/1 Hex/EtOAc) | M+H 504.5 | | A6, B1 |

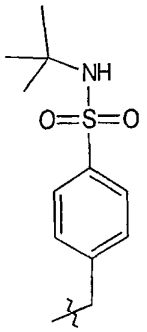
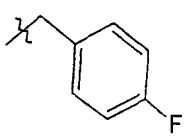
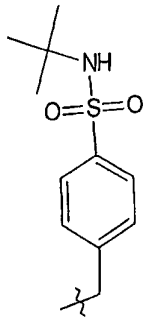
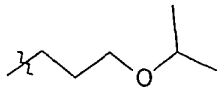
| Ex. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp (°C) | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 90 | H |  |  | H | TLC Rf = 0.29 (4/1 CH2Cl2/MeOH) | M+H 472 | | A6, B1, C1 |
| 91 | H |  |  | H | TLC Rf = 0.54 (9/1 CH2Cl2/MeOH) | M+H 486 | | A6, B1 |
| 92 | H |  |  | H | TLC Rf =0.18 (9/1 CH2Cl2/MeOH) | M+H 546 | | A6, B1 |

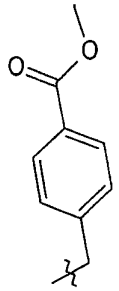
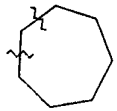
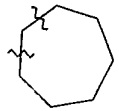
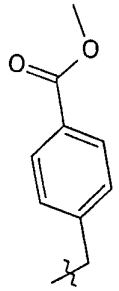
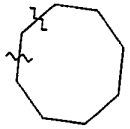
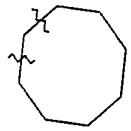
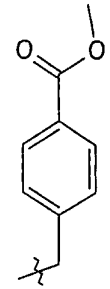
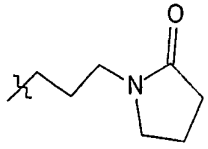
| Ex. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp (°C) | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 93 |  |  |  |  | TLC Rf = 0.06 (9/1 CH2Cl2/MeOH) | M+H 470 | | A6, B1 |
| 94 |  |  |  |  | | M+H 442 | | A6, B1 |

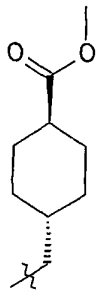
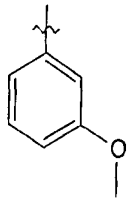
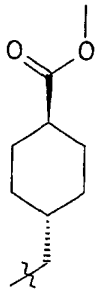
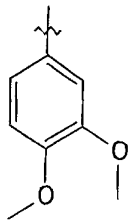
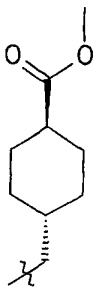
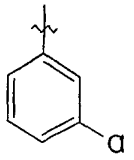
| Ex. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp (°C) | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 95 | H |  |  | H | TLC Rf = 0.30 (3/2 Hex/EtOAc) | M+H 503 | | A6, B1, C1, C3 |
| 96 | H |  |  | H | TLC Rf = 0.1 (3/2 Hex/EtOAc) | M+H 429 | | A6, B1 |
| 97 | H |  |  | H | TLC Rf = 0.28 (3/2 HE/EtOAc) | M+H 387 | | A6, B1 |

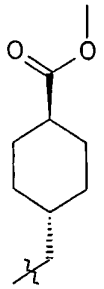
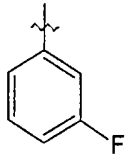
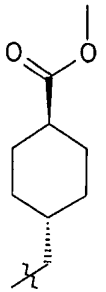
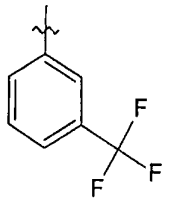
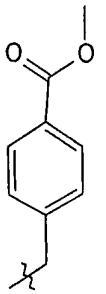
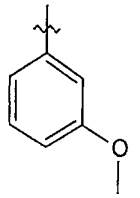
| Ex. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp (°C) | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 98 | H |  |  | H | TLC Rf = 0.25 (3/2 Hex/EtOAc) | M+H 413 | | A6, B1 |
| 99 | H |  |  | H | TLC (1/1 EtOAc/Hex) Rf = 0.08 | 486.3 | 217 | A6, A12, B1 |
| 100 | H |  |  | H | TLC (1/1 EtOAc/Hex) Rf = 0.20 | 549.5 | 216 | A6, A12, B1 |

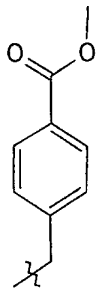
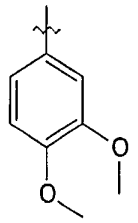
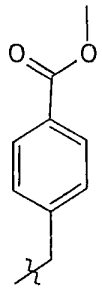
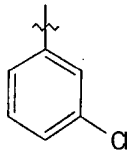
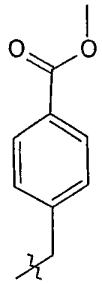
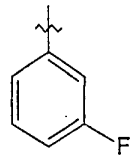
| Ex. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp (°C) | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 101 | H |  |  | H | TLC (1/4 EtOAc/Hex) Rf = 0.22 | 537.2 | 161 | A6, A12, B1 |
| 102 | H |  |  | H | TLC (1/1 EtOAc/Hex0 Rf = 0.24 | 516.8 | 221-223 | A6, A12, B1 |

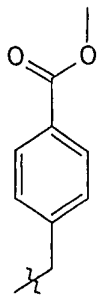
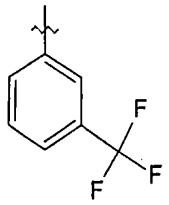
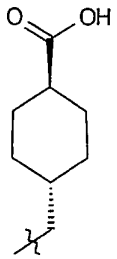
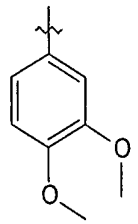
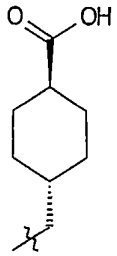
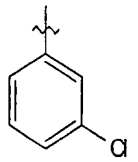
| Ex. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp (°C) | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 103 | H |  |  | H | TLC (1/1 EtOAc/Hex) Rf = 0.33 | 528.9 | >225 | A6, A12, B1 |
| 104 | H |  |  | H | TLC (1/1 EtOAc/Hex) Rf = 0.25 | 520.9 | NA | A6, A12, B1 |

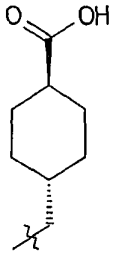
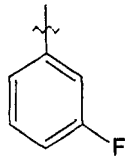
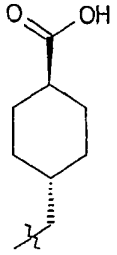
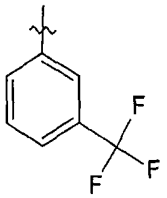
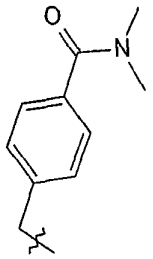
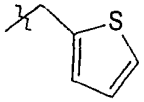
| Ex. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp (°C) | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 105 | H |  |  |  | TLC (9/1 EtOAc/MeOH) Rf = 0.73 | 425.4 | 143-4 | A6, B1 |
| 106 | H |  |  |  | TLC (8/2 CH2Cl2/MeOH) Rf=0.70 | 439.4 | 162-3 | A6, B1 |
| 107 | H |  |  | H | TLC (1/4 MeOH/CH2Cl2) Rf = 0.8 | 468.4 | oil | A6, B1 |

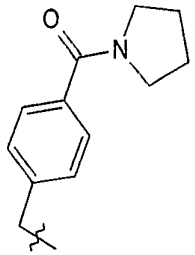
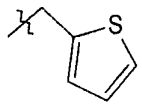
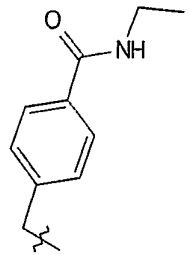
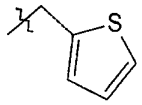
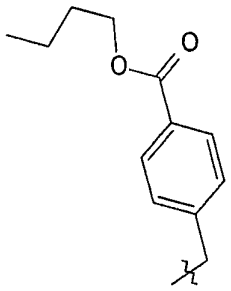
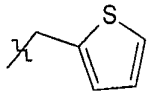
| Ex. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp (°C) | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 108 | H |  |  | H | TLC Rf (95:5 CH2Cl2/MeOH) 0.64 | 455.5 | 216-218 | A6, B1 step 1, B6 step 1 |
| 109 | H |  |  | H | TLC Rf (95:5 CH2Cl2/MeOH) 0.44 | 485.5 | 196-199 | A6, B1 step 1, B6 step 1 |
| 110 | H |  |  | H | TLC Rf (95:5 CH2Cl2/MeOH) 0.54 | 459.4 | 199-201 | A6, B1 step 1, B6 step 1 |

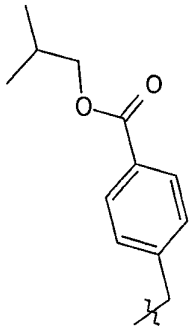
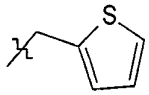
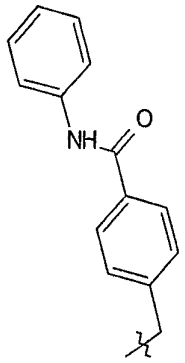
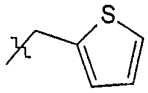
| Ex. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp (°C) | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 111 | H |  |  | H | TLC Rf (95:5 CH2Cl2/MeOH) 0.65 | 443.4 | 203-207 | A6, B1 step 1, B6 step 1 |
| 112 | H |  |  | H | TLC Rf (95:5 CH2Cl2/MeOH) 0.72 | 493.5 | 181-184 | A6, B1 step 1, B6 step 1 |
| 113 | H |  |  | H | TLC Rf (50:50 EtOAc/Hex)0.64 | 449.2 | 143-146 | A6, B1 step 1, B6 step 1 |

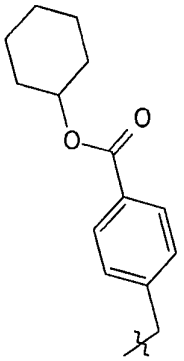
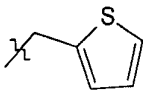
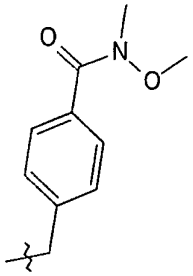
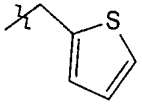
| Ex. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp (°C) | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 114 | H |  |  | H | TLC Rf (95:5 CH2Cl2/MeOH) 0.51 | 479.2 | 171-176 | A6, B1 step 1, B6 step 1 |
| 115 | H |  |  | H | TLC Rf(50:50 EtOAc/Hex) 0.59 | 453.2 | 154-157 | A6, B1 step 1, B6 step 1 |
| 116 | H |  |  | H | TLC Rf (50:50 EtOAc/Hex) 0.58 | 437.2 | 150-152 | A6, B1 step 1, B6 step 1 |

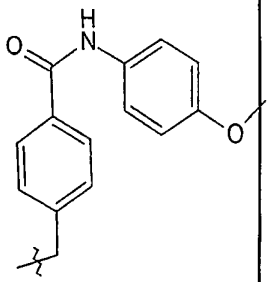
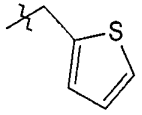
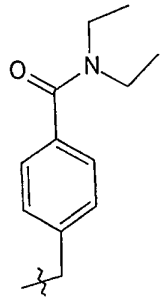
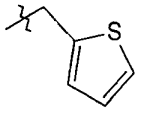
| Ex. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp (°C) | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 117 | H |  |  | H | TLC Rf (50:50 EtOAc/Hex) 0.60 | 487.2 | 160-165 | A6, B1 step 1, B6 step 1 |
| 118 | H |  |  | H | HPLC RT (90:10 - 10:90 H2O/CH3CN) 2.56 MIN. | 471.5 | 284-287 | A6, B1 step 1, B6 |
| 119 | H |  |  | H | HPLC RT (90:10 - 10:90 H2O/CH3CN) 2.93 | 445.5 | 288-293 | A6, B1 step 1, B6 |

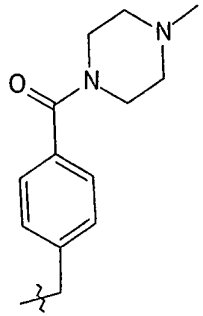
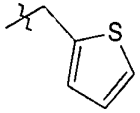
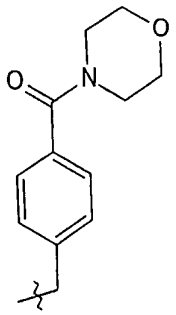
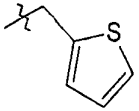
| Ex. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp (°C) | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 120 | H |  |  | H | HPLC RT(90:10 - 10:90 H2O/CH3CN) 2.78 MIN. | 429.5 | | A6, B1 step 1, B6 |
| 121 | H |  |  | H | HPLC RT (90:10 - 10:90 H2O/CH3CN) 3.01 MIN. | 479.5 | | A6, B1 step 1, B6 |
| 122 | H |  |  | H | TLC Rf (EtOAc 100) 0.15 | 452.3 | | A6, B1, C1, C2 |

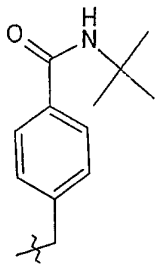
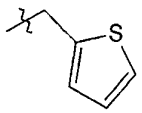
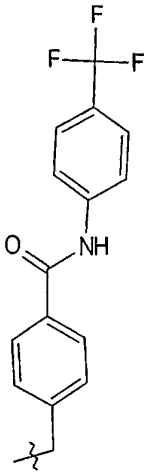
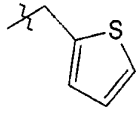
| Ex. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp (°C) | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 123 | H |  |  | H | TLC Rf (EtOC 100) 0.15 | 478.3 | 241-242 | A6, B1, C1, C2 |
| 124 | H |  |  | H | TLC Rf (EtOAc 100) 0.29 | 452.2 | 240-241 | A6, B1, C1, C2 |
| 125 | H |  |  | H | TLC Rf (EtOAc/Hex 50:50) 0.35 | 481.4 | 92-93 | A6, B1, C1, C3 |

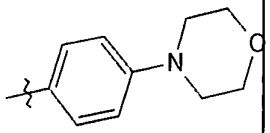
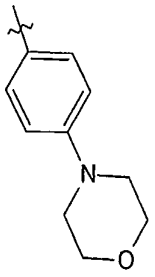
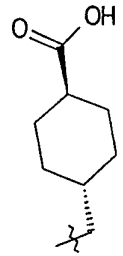
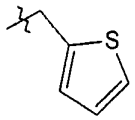
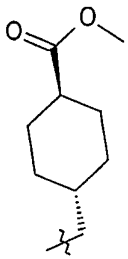
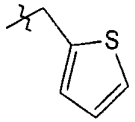
| Ex. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp (°C) | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 126 | H |  |  | H | TLC Rf (EtOAc/Hex 50:50) 0.39 | 481.4 | 97-98 | A6, B1, C1, C3 |
| 127 | H |  |  | H | TLC Rf (EtOAc 100) 0.72 | 500.3 | 138-139 | A6, B1, C1, C2 |

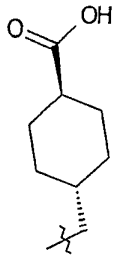
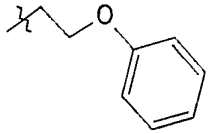
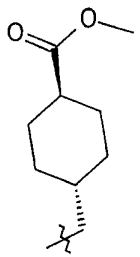
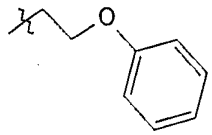
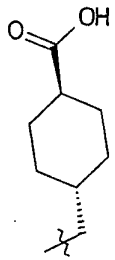
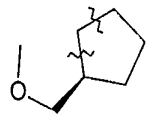
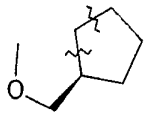
| Ex. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp (°C) | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 128 | H |  |  | H | TLC Rf (EtOAc/Hex 50:50) 0.39 | 507.4 | 105-106 | A6, B1, C1, C3 |
| 129 | H |  |  | H | TLC Rf (EtOAc 100) 0.46 | 468.3 | 175-178 | A6, B1, C1, C2 |

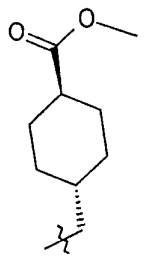
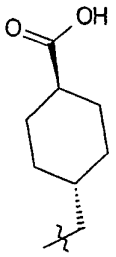
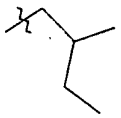
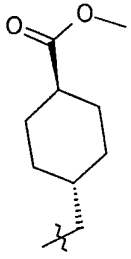
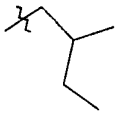
| Ex. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp (°C) | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 130 | H |  |  | H | TLC Rf (100 EtOAc) 0.47 | 530.1 | 139 | A6, B1, C1, C2 |
| 131 | H |  |  | H | TLC Rf (100 EtOAc) 0.31 | 480.1 | 159-160 | A6, B1, C1, C2 |

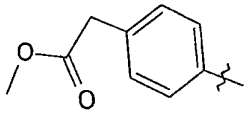
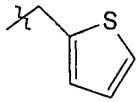
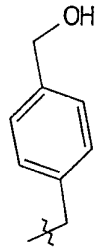
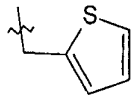
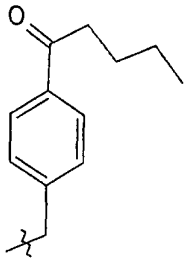
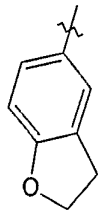
| Ex. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp (°C) | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 132 | H |  |  | H | HPLC RT (55% CH3CN) 2.04 MIN | 507.1 | 137-138 | A6, B1, C1, C2 |
| 133 | H |  |  | H | TLC Rf (100 EtOAc) 0.2 | 494.1 | 250-251 | A6, B1, C1, C2 |

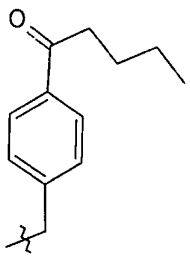
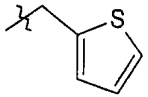
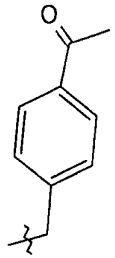
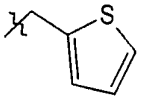
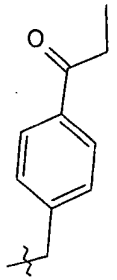
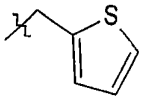
| Ex. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp (°C) | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 134 | H |  |  | H | TLC Rf (100 EtOAc) 0.55 | 480.4 | 120-121 | A6, B1, C1, C2 |
| 135 | H |  |  | H | TLC (100 EtOAc) 0.61 | 568.4 | 138-139 | A6, B1, C1, C2 |

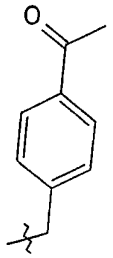
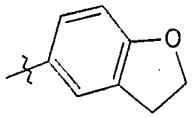
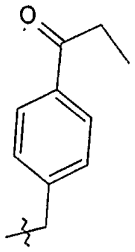
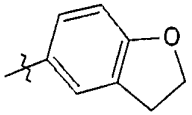
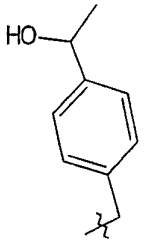
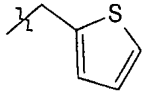
| Ex. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp (°C) | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 136 | H |  |  | H | TLC (100 EtOAc) 0.45 | 517.6 | 115-116 | A6, B12 |
| 137 | H |  |  | H | TLC (1/1 MeOH/EtOAc) Rf = 0.57 | 431.3 | >220 | A6, B1, C1 |
| 138 | H |  |  | H | TLC (9/1 EtOAc/Hex) Rf = 0.68 | 445.4 | 143-145 | A6, B1 |

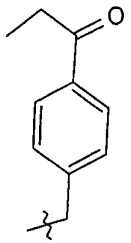
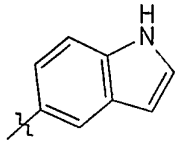
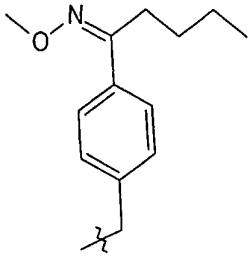
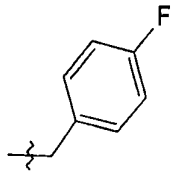
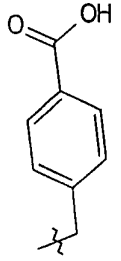
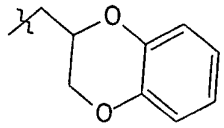
| Ex. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp (°C) | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 139 | H |  |  | H | TLC (1/1 EtOAc/MeOH) Rf = 0.61 | 455.4 | 210-212 | A6, B1, C1 |
| 140 | H |  |  | H | TLC (9/1 EtOAc/MeOH) Rf = 0.64 | 469.5 | 147-149 | A6, B1 |
| 141 | H |  |  |  | TLC (1/1 MeOH/EtOAc) Rf = 0.64 | 433.5 | 190-192 | A6, B1, C1 |

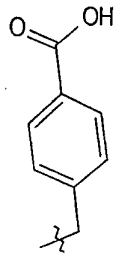
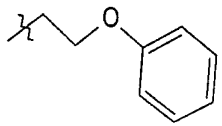
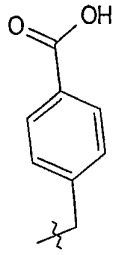
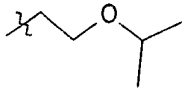
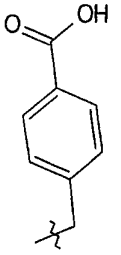
| Ex. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp (°C) | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 142 | H |  |  |  | TLC (9/1 EtOAc/MeOH) Rf = 0.54 | 447.5 | 74-76 | A6, B1 |
| 143 | H |  |  | H | TLC (1/1 EtOAc/MeOH) Rf = 0.54 | 405.5 | >220 | A6, B1, C1 |
| 144 | H |  |  | H | TLC (9/1 EtOAc/MeOH) Rf = 0.46 | 419.5 | 135-137 | A6, B1 |

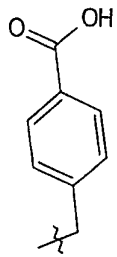
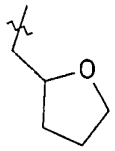
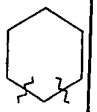
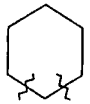
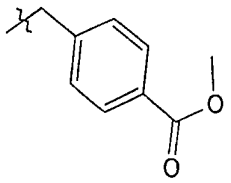
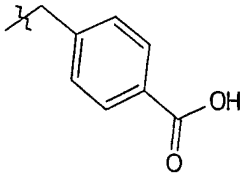
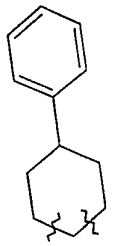
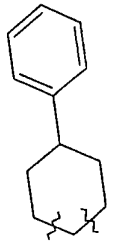
| Ex. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp (°C) | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 145 | H |  |  | H | TLC (100% EtOAc) Rf = 0.78 | 439.3 | 167-170 | A6, B1 |
| 146 | H |  |  | H | TLC (10% MeOH/90% EtOAc) Rf = 0.26 | 411.1 | | A6, B1, C8 |
| 147 | H |  |  | H | TLC (EtOAc) Rf = 0.50 | 487.3 | >205 | A6, A13, B1 |

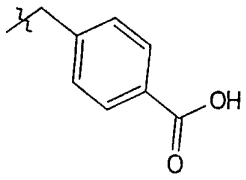
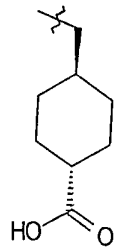
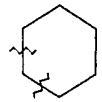
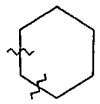
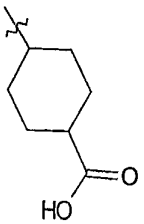
| Ex. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp (°C) | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 148 | H |  |  | H | TLC (1/1 EtOAc/Hex) Rf = 0.16 | 465.1 | 157-159 | A6, A13, B1 |
| 149 | H |  |  | H | TLC (100% EtOAc) Rf = 0.50 | 423 | 200-203 | A6, A13, B1 |
| 150 | H |  |  | H | TLC (100% EtOAc) Rf = 0.50 | 437.5 | 176-177 | A6, A13, B1 |

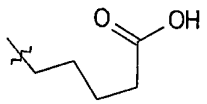
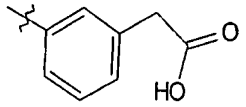
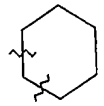
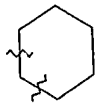
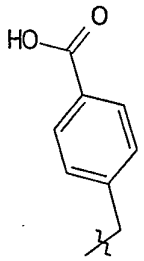
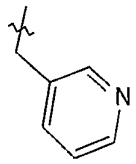
| Ex. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp (°C) | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 151 | H |  |  | H | TLC 100% EtOAc) Rf = 0.6 | 445.5 | >210 | A6, A13, B1 |
| 152 | H |  |  | H | TLC (100% EtOAc) Rf = 0.63 | 459.6 | 166-168 | A6, A13, B1 |
| 153 | H |  |  | H | TLC (3/7 EtOAc/Hex) Rf = 0.15 | 439.3 | 168-170 | A6, B1, B7 |

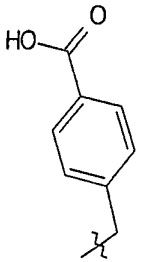
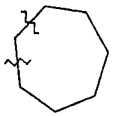
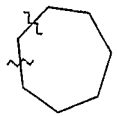
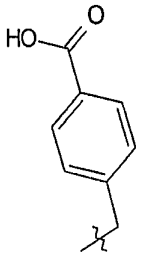
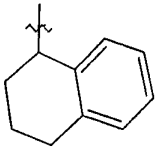
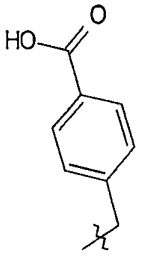
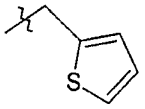
| Ex. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp (°C) | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 154 | H |  |  | H | TLC (9/1 EtOAc/MeOH) Rf = 0.18 | 456.4 | 168-170 | A6, A13, B1 |
| 155 | H |  |  | H | TLC (1/1 EtOAc/Hex) Rf = 0.32 | 506.1 | – | A6, A14, B1 |
| 156 | H |  |  | H | HPLC RT =2.48 min | 477.2 | | A6, B14 |

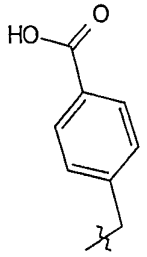
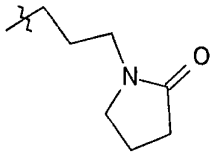
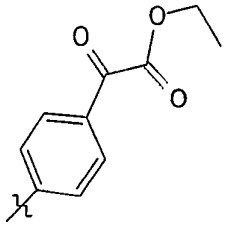
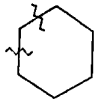
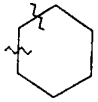
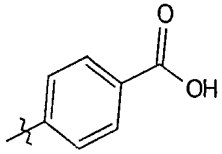
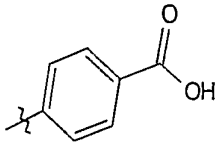
| Ex. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp (°C) | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 157 | H |  |  | H | HPLC RT =2.59 min | 449.0 | | A6, B14 |
| 158 | H |  |  | H | HPLC RT =2.41 min | 415.1 | | A6, B14 |
| 159 | H |  |  | H | HPLC RT =2.56 min | 397.1 | | A6, B14 |

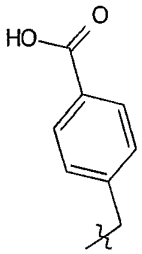
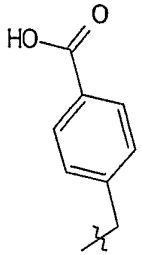
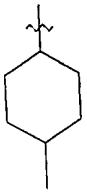
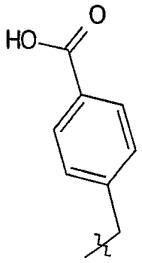
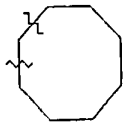
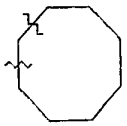
| Ex. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp (°C) | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 160 | H |  |  | H | HPLC RT =2.30 min | 413.1 | | A6, B14 |
| 161 |  |  |  | H | 0.17 25%EtOAc/Hex | 411 @ 3.25 min | | A6, B3 |
| 162 | H |  |  |  | 0.21 10% MeOH/EtOAc | 473 @ 3.20 min | | A6, B2 step 1, B7, B3 step 3 |

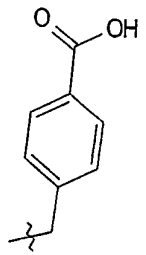
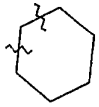
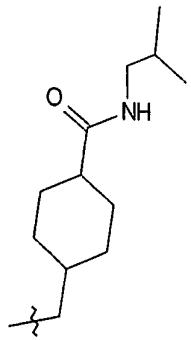
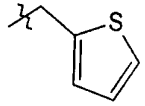
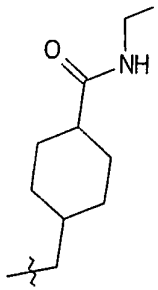
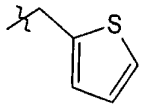
| Ex. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp (°C) | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 163 | H |  | | | 0.40 25%MeOH/EtOAc | 357 @ 2.82 min | | A6, B2 step 1, B9, B3 step 3 |
| 164 | H |  |  |  | 0.48 10%MeOH/EtOAc | 403 @ 3.06 min | | A6, B2 step 1, B8 |
| 165 | H |  |  |  | 0.40 10%MeOH/EtOAc | 389 @ 3.05 min | | A6, B2 step 1, B8 |

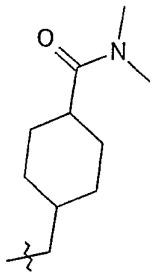
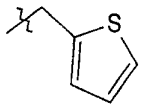
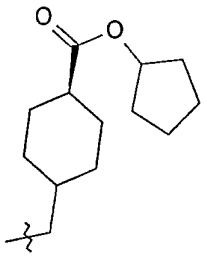
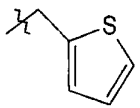
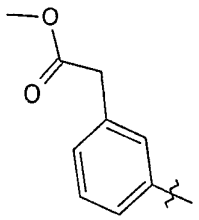
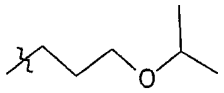
| Ex. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp (°C) | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 166 | H |  |  |  | 0.27 25%MeOH/EtOAc | 363 @ 2.92 min | | A6, B2 |
| 167 | H |  |  |  | 0.30 25%MeOH/EtOAc | 397 @ 2.89 min | | A6, B2 |
| 168 | H |  |  | H | | 420 @ 2.36 min | >290 | A6, B2 step 1, D2 |

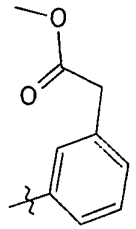
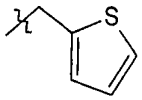
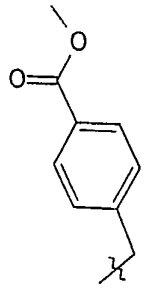
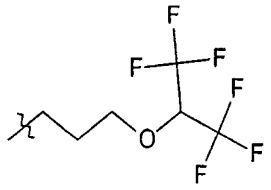
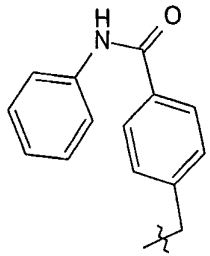
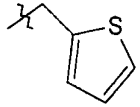
| Ex. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp (°C) | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 169 | H |  |  |  | | 411 @ 2.94 min | >260 | A6, B2 step 1, D2 |
| 170 | H |  |  | H | | 459 @ 3.15 min | >270 | A6, B2 step 1, D2 |
| 171 | H |  |  | H | 0.80 33%MeOH/EtOAc | 425 @ 2.79 min | >270 | A6, B2 step 1, D2 |

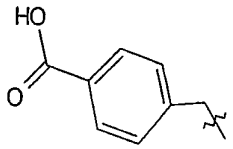
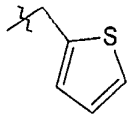
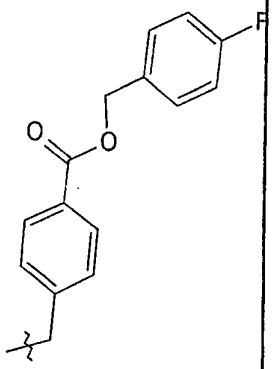
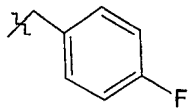
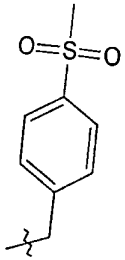
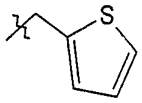
| Ex. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp (°C) | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 172 | H |  |  | H | | 454 @ 2.74 min | >250 | A6, B2 step 1, D2 |
| 173 | H |  |  |  | 0.64 20%EtOAc/Hex | 477 @ 3.21 min | 240 | A6, A15, B4, B8 |
| 174 | H |  |  | H | | 435 @ 2.85 min | | A6, B5, B3 step3 |

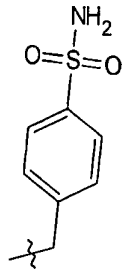
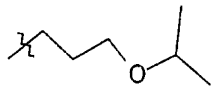
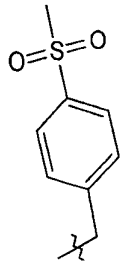
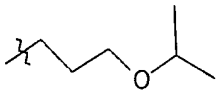
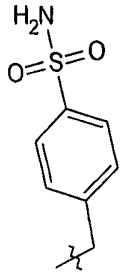
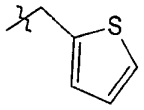
| Ex. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp (°C) | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 175 |  |  |  |  | | 383 @ 2.32 min | 170 | A6, B2 step 1, D2 |
| 176 |  |  |  |  | | 425 @ 2.50 min | >270 | A6, B2 step 1, D2 |
| 177 |  |  |  |  | | 425 @ 2.33 min | >270 | A6, B2 step 1, D2 |

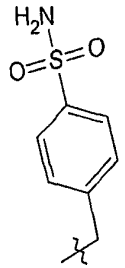
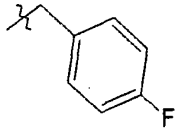
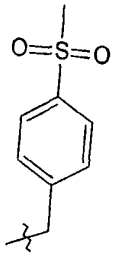
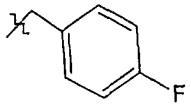
| Ex. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp (°C) | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 178 | H |  |  |  | 0.15 20%MeOH/EtOAc | 397 @ 2.95 min | | A6, B2, B3 step3 |
| 179 | H |  |  | H | TLC (1/9 MeOH/CHCL3) Rf = 0.31 | 486.5 | | A6, B1, C1, C2 |
| 180 | H |  |  | H | TLC (1/9 MeOH/CHCL3) Rf = 0.28 | 458.4 | | A6, B1, C1, C6 |

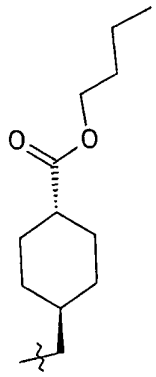
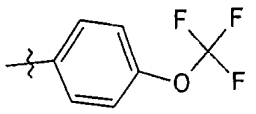
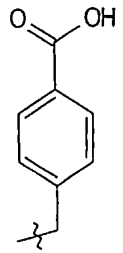
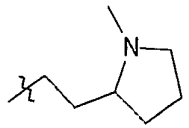
| Ex. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp (°C) | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 181 | H |  |  | H | TLC (1/9 MeOH/CHCL3) Rf = 0.33 | 458.4 | | A6, B1, C1, C6 |
| 182 | H |  |  | H | TLC (1/9 MeOH/CHCL3) Rf = 0.26 | 499.4 | 205-206 | A6, B1, C1, C6 |
| 183 | H |  |  | H | TLC (1/1 EtOAc/Hex) Rf = 0.44 | 352.1 | | A6, B1 |

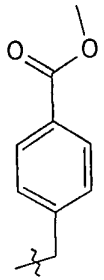
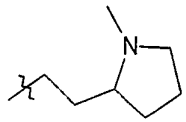
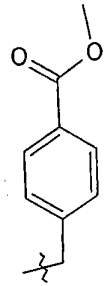
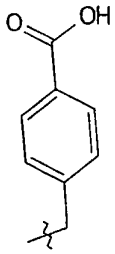
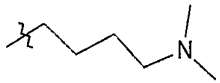
| Ex. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp (°C) | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 184 | H |  |  | H | TLC (40% EtOAc/60% Hex) Rf = 0.53 | 348.1 | 129-131 | A6, B1 |
| 185 | H |  |  | H | | 313.5 | 182-183 | A6, A11, B1 |
| 186 | H |  |  | H | TLC (1/1 EtOAc/Hex) Rf = 0.52 | 500.3 | 195-197 | A6, B1, C1, C6 |

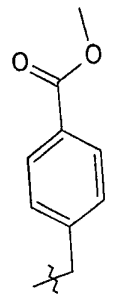
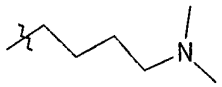
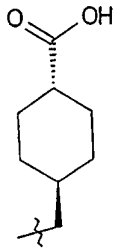
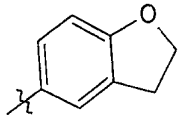
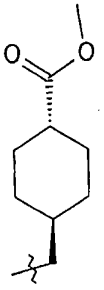
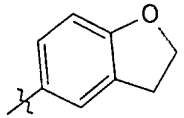
| Ex. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp (°C) | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 187 | H |  |  | H | > 80% PURE - TLC (1/1 EtOAc/Hex) Rf = 0.77 | 425.3 | >225 | A6, B1, C1 |
| 188 | H |  |  | H | TLC (1/1 EtOAc/Hex) Rf = 0.27 | 545.3 | 178-179 | A6, B1 |
| 189 | H |  |  | H | TLC (1/1 EtOAc/Hex) Rf = 0.15 | 459.2 | >225 | A6, B1 |

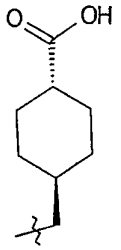
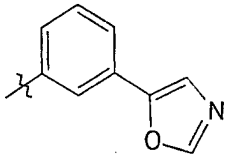
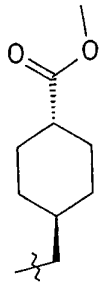
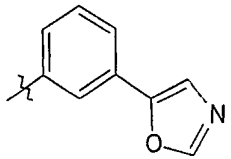
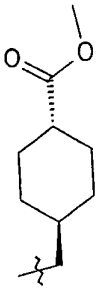
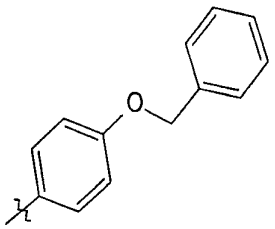
| Ex. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp (°C) | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 190 | H |  |  | H | TLC (1/1 EtOAc/Hex) Rf = 0.05 | 464.3 | >225 | A6, B1 |
| 191 | H |  |  | H | TLC ( 1/1 EtOAc/Hex) Rf = 0.32 | 463.3 | >225 | A6, B1 |
| 192 | H |  |  | H | TLC (1/1 EtOAc/Hex) 0.30 | 460.1 | >225 | A6, B1 |

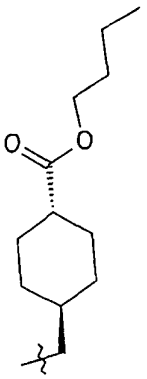
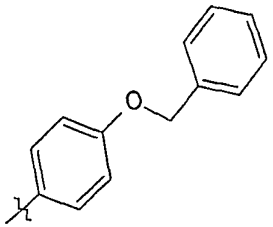
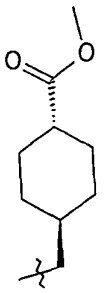
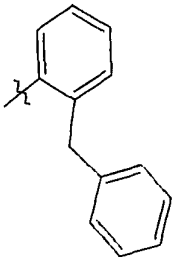
| Ex. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp (°C) | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 193 | H |  |  | H | TLC (1/1 EtOAc/Hex) Rf = 0.34 | 472.3 | >225 | A6, B1 |
| 194 | H |  |  | H | TLC (1/1 EtOAc/Hex) Rf = 0.09 | 471.3 | >225 | A6, B1 |

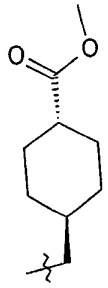
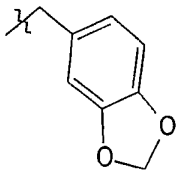
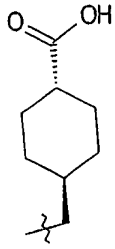
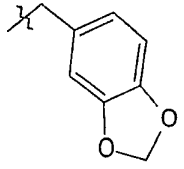
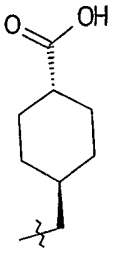
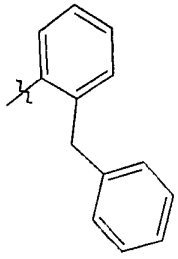
| Ex. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp (°C) | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 195 | H |  |  | H | TLC Rf =0.78 (1/1 Hex/EtOAc) | 551.5 | | A6, B1, C1, C3 |
| 196 | H |  |  | H | HPLC RT = 1.65 (4ML/MIN 20-70%CH3CN/H20) | 440.4 | | A6, B1, C1 |

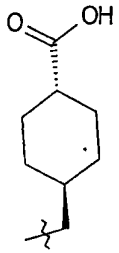
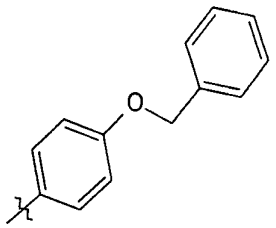
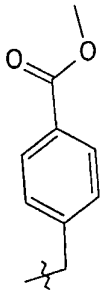
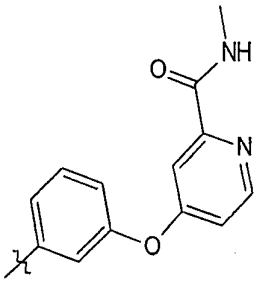
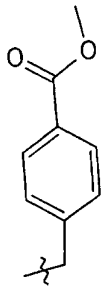
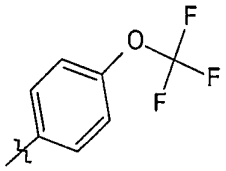
| Ex. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp (°C) | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 197 | H |  |  | H | HPLC RT = 1.59 4ML/MIN 20-60%CH3CN/H20) | 454.4 | | A6, B1 |
| 198 | H |  |  |  | HPLC RT = 2.45 (4ML/MIN 10-80% CH3CN/H20) | 397.4 | | A6, B1 |
| 199 | H |  |  | H | HPLC RT = 1.59 (20-60% CH3CN/H20) | 428.2 | | A6, B1 |

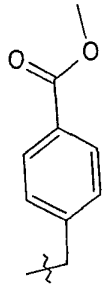
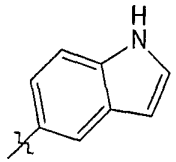
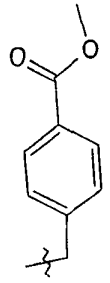
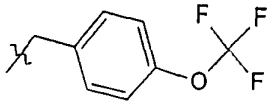
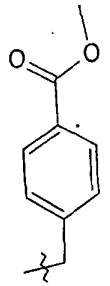
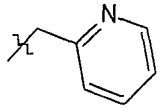
| Ex. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp (°C) | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 200 | H |  |  | H | HPLC Rf = 1.91 (4ML/MIN 10-80% CH3CN/H20) | 442.3 | | A6, B1 |
| 201 | H |  |  | H | TLC Rf = .28 (100% EtOAc) | 453.5 | | A6, B1, C1 |
| 202 | H |  |  | H | TLC Rf = 0.76 (100% EtOAc) | 467.5 | | A6, B1 |

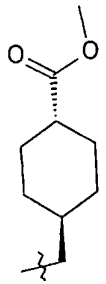
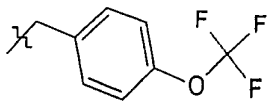
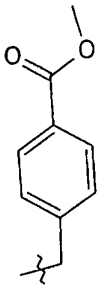
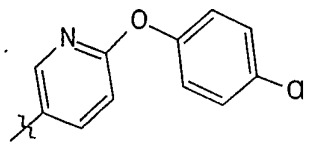
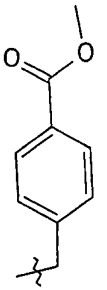
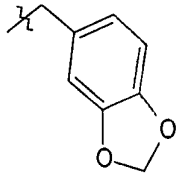
| Ex. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp (°C) | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 203 | H |  |  | H | TLC Rf = 0.56 (100% EtOAc) | 478.5 | | A6, B1, C1 |
| 204 | H |  |  | H | TLC Rf = 0.85 (100% EtOAc) | 492.5 | | A6, B1, C1 |
| 205 | H |  |  | H | TLC Rf = 0.38 (1/1 Hex/EtOAc) | 531.5 | | A6, B1 |

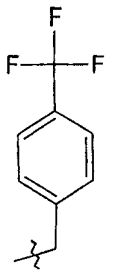
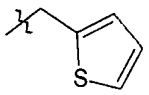
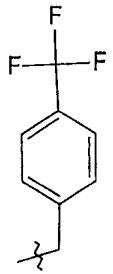
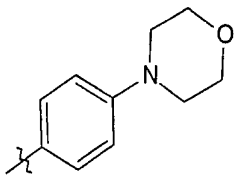
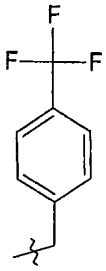
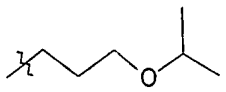
| Ex. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp (°C) | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 206 | H |  |  | H | TLC Rf = 0.44 (1/1 Hex/EtOAc) | 573.5 | | A6, B1 |
| 207 | H |  |  | H | TLC Rf = 0.53 (1/1 Hex/EtOAc) | 515.5 | | A6, B1 |

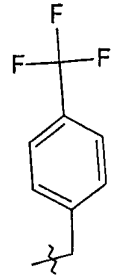
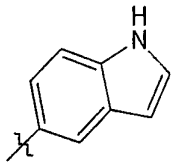
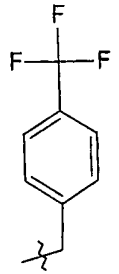
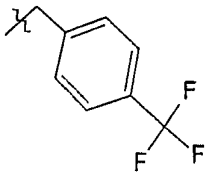
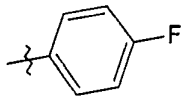
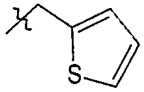
| Ex. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp (°C) | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 208 | H |  |  | H | TLC Rf = 0.72 (100% EtOAc) | 483.5 | | A6, B1 |
| 209 | H |  |  | H | TLC Rf = 0.56 (100%EtOAc) | 469.4 | | A6, B1 |
| 210 | H |  |  | H | TLC Rf = 53 (100% EtOAc) | 501.5 | | A6, B1, C1 |

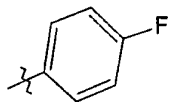
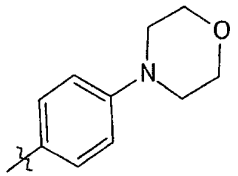
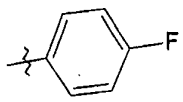
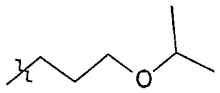
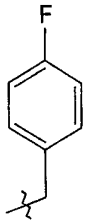
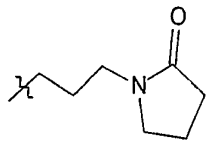
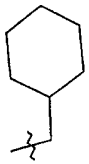
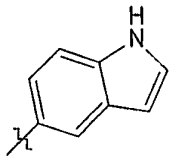
| Ex. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp (°C) | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 211 | H |  |  | H | TLC Rf = 0.53 (100% EtOAc) | 517.4 | | A6, B1, C1 |
| 212 | H |  |  | H | TLC Rf = 0.21 (1/1 Hex/EtOAc) | 569.5 | | A6, B1 |
| 213 | H |  |  | H | TLC Rf = 0.71 (1/1 Hex/EtOAc) | 503.5 | | A6, B1 |

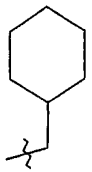
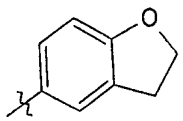
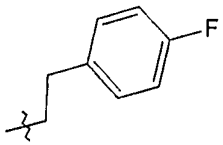
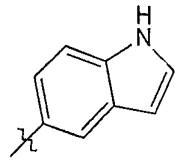
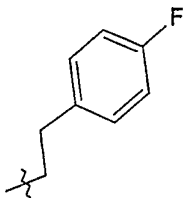
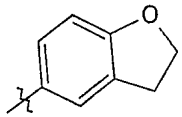
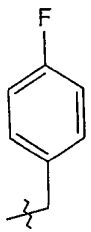
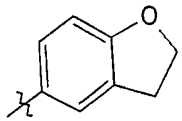
| Ex. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp (°C) | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 214 | H |  |  | H | TLC Rf = 0.71 (1/1 Hex/EtOAc) | 458.5 | | A6, B1 |
| 215 | H |  |  | H | TLC Rf=0.21 (1/1 Hex/EtOAc) | 517.4 | | A6, B1 |
| 216 | H |  |  | H | TLC Rf = 0.09 (100% EtOAc) | 434.4 | | A6, B1 |

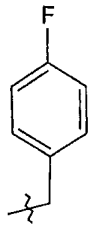
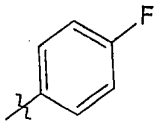
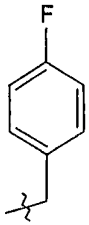
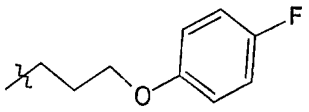
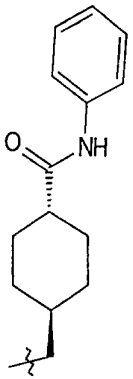
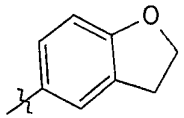
| Ex. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp (°C) | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 217 | H |  |  | H | TLC Rf = 0.43 (1/1 EtOAc/Hex) | 523.5 | | A6, B1 |
| 218 | H |  |  | H | TLC Rf = 0.42 (1/1 Hex/EtOAc) | 546.5 | | A6, B1 |
| 219 | H |  |  | H | TLC Rf = 0.54 (100% EtOAc) | 477.1 | | A6, B1 |

| Ex. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp (°C) | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 220 | H |  |  | H | TLC Rf = 0.32 (1/1 Hex/EtOAc) | 449.3 | | A6, B1 |
| 221 | H |  |  | H | TLC Rf = 0.22 (1/1 Hex/EtOAc) | 514.5 | | A6, B1 |
| 222 | H |  |  | H | TLC Rf = 0.17 (1/1 Hex/EtOAc) | 453.4 | | A6, B1 |

| Ex. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp (°C) | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 223 | H |  |  | H | TLC Rf = 0.23 (1/1 Hex/EtOAc) | 468.5 | | A6, B1 |
| 224 | H |  |  | H | TLC Rf = 0.23 (1/1 Hex/EtOAc) | 511.4 | | A6, B1 |
| 225 | H |  |  | H | TLC Rf = 0.55 (1/1 Hex/EtOAc) | 385.3 | | A6, B1 |

| Ex. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp (°C) | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 226 | H |  |  | H | TLC Rf = 0.29 (1/1 Hex/EtOAc) | 450.4 | | A6, B1 |
| 227 | H |  |  | H | TLC Rf = 0.48 (1/1 Hex/EtOAc) | 389.3 | | A6, B1 |
| 228 | H |  |  | H | TLC = Rf= 0.64 (5/1 EtOAc/MeOH) | 428.4 | | A6, B1 |
| 229 | H |  |  | H | TLC Rf = 0.19 (1/1 Hex/EtOAc) | 406.4 | | A6, B1 |

| Ex. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp (°C) | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 230 | H |  |  | H | TLC Rf = 0.39 (1/1 Hex/EtOAc) | 409.6 | | A6, B1 |
| 231 | H |  |  | H | TLC Rf = 0.13 (1/1 Hex/EtOAc) | 432.2 | | A6, B1 |
| 232 | H |  |  | H | TLC Rf = 0.28 (1/1 Hex/EtOAc) | 435.6 | | A6, B1 |
| 233 | H |  |  | H | TLC Rf = 0.40 (1/1 Hex/EtOAc) | 421.3 | | A6, B1 |

| Ex. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp (°C) | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 234 | H |  |  | H | TLC Rf=0.61 (1/1 Hex/EtOAc) | 397.3 | | A6, B1 |
| 235 | H |  |  | H | TLC Rf = 0.16 (1/1 Hex/EtOAc) | 455.3 | | A6, B1 |
| 236 | H |  |  | H | TLC Rf = 0.38 (9/1 CH2Cl2/MeOH) | 528.4 | | A6, B1, C2 |

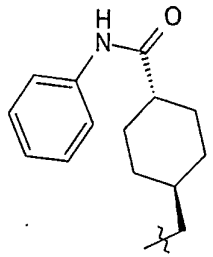
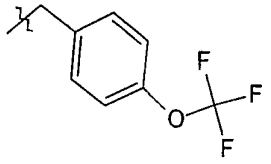
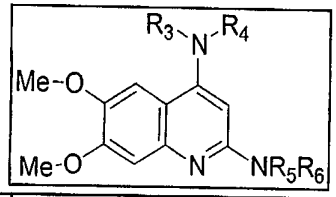
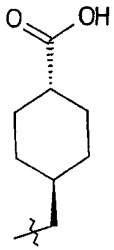
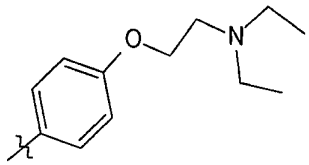
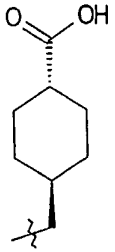
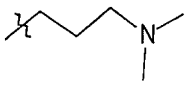
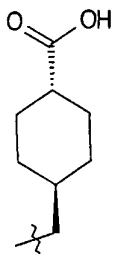
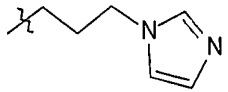
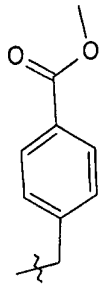
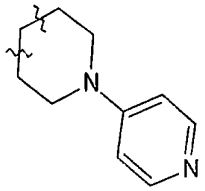
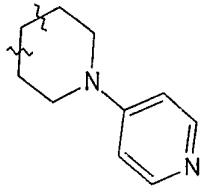
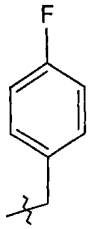
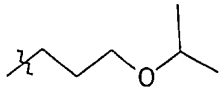
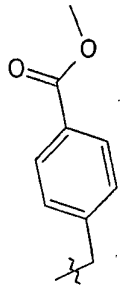
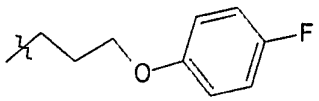
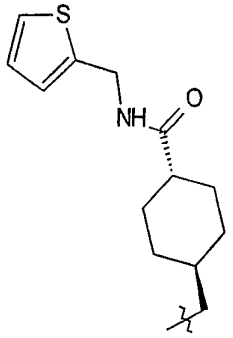
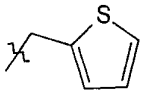
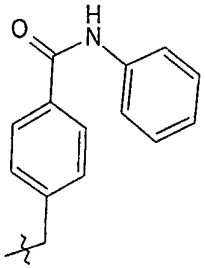
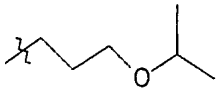
| Ex. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp (°C) | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 237 | H |  |  | H | TLC Rf = 0.28 (9/1 CH2Cl2/MeOH) | 584.6 | | A6, B1 |

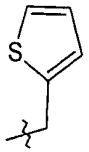
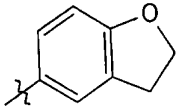
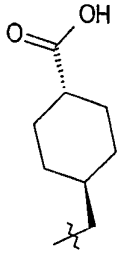
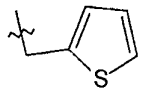
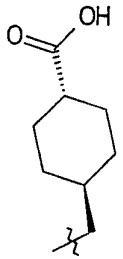
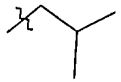
**Table 2. Dimethoxy Quinazolines**

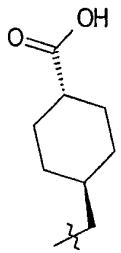
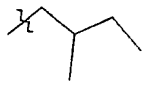
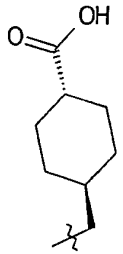
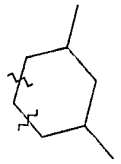
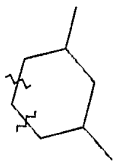
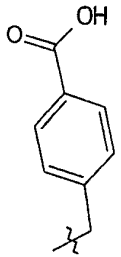
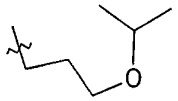


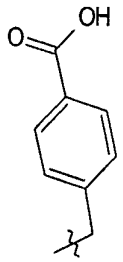
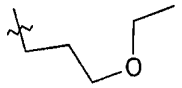
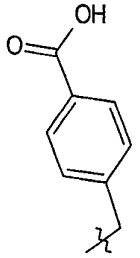
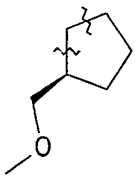
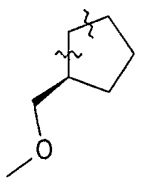
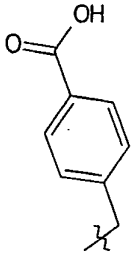
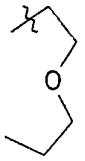

| Ex. No. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 238 | H |  |  | H | HPLC RT: 1.89 (98%H20 TO 98% CH3CN) | 552 | | A10, B1 |
| 239 | H |  |  | H | HPLC RT: 1.56 (98% H20 - 98% CH3CN) | 446 | | B1 |

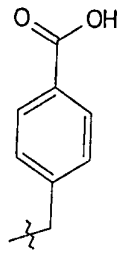
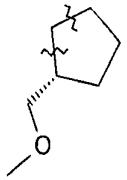
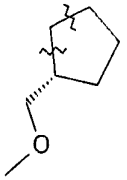
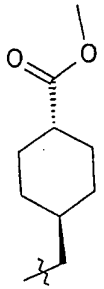
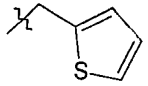
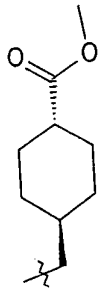
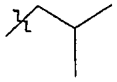
| Ex. No. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 240 | H |  |  | H | HPLC RT=1.65 (98%H20-98% CH3CN) | 469 | | B1 |
| 241 | H |  |  |  | TLC Rf = 0.41 (9/1 CH2Cl2/MeOH) | 515 | | B1 |
| 242 | H |  |  | H | HPLC RT = 2.58(98%H 20-98%CH3CN ) | 429 | | B1 |

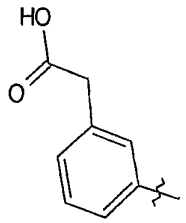
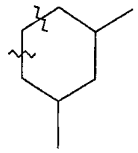
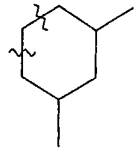
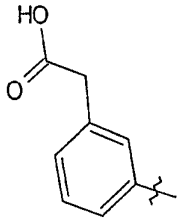
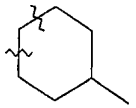
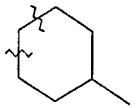
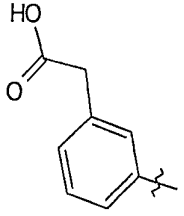
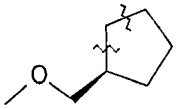
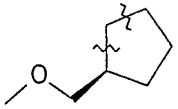
| Ex. No. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 243 | H |  |  | H | HPLC RT=2.68 (10-90% CH3CN-H20) | 521 | | B1 |
| 244 | H |  |  | H | | 552 | | B1 |
| 245 | H |  |  | H | TLC (10% MeOH/90% EtOAc) Rf = 0.14 | 530.3 | 197-198 | B1, C1, C2 |

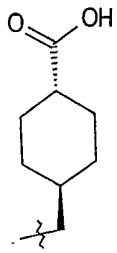
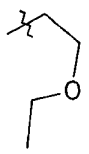
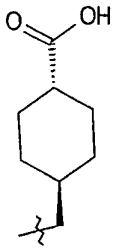
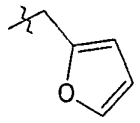
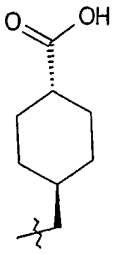
| Ex. No. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 246 | H |  |  | H | TLC (EtOAc) Rf = 0.32 | 435.2 | 149.5-150 | B1 |
| 247 | H |  |  | H | HPLC Ret Time 2.45 | 457 | | B14 |
| 248 | H |  |  | H | 2.48 | 417 | | B14 |

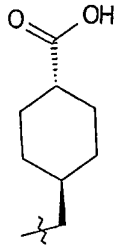
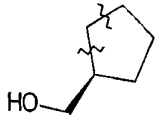
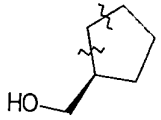
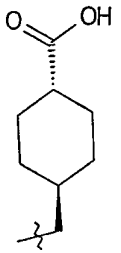
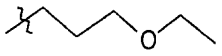
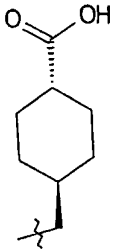
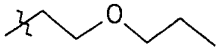
| Ex. No. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 249 | H |  |  | H | 2.58 | 431 | | B14 |
| 250 | H |  |  |  | 2.78 | 457 | | B14 |
| 251 | H |  |  | H | 1.39 | 455 | | B14 |

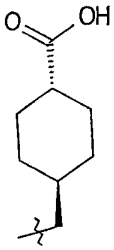
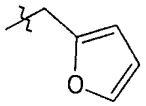
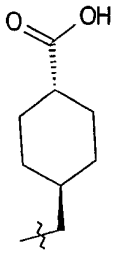
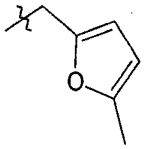
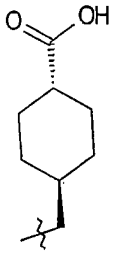
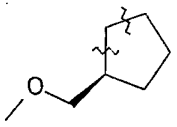
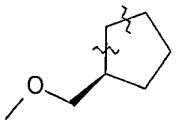
| Ex. No. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 252 | H |  |  | H | 1.48 | 441 | | B14 |
| 253 | H |  |  |  | 1.45 | 453 | | B14 |
| 254 | H |  |  | H | 0.61 | 441 | | B14 |

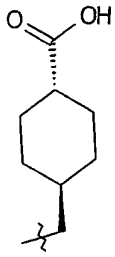
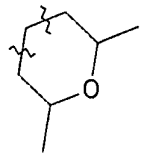
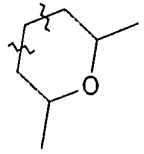
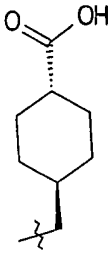
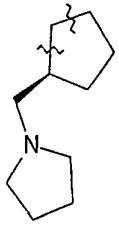
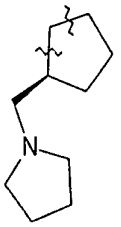
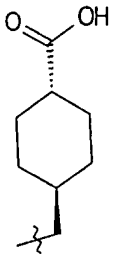
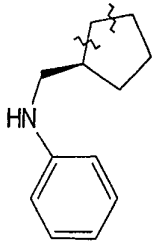
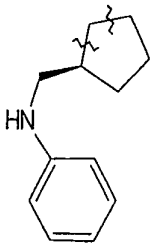
| Ex. No. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 255 | H |  |  |  | 2.45 | 453 | | B14 |
| 256 | H |  |  | H | 2.85 | 471 | | B14 |
| 257 | H |  |  | H | 2.89 | 431 | | B14 |

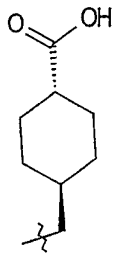
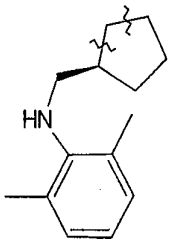
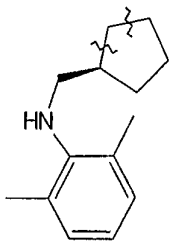
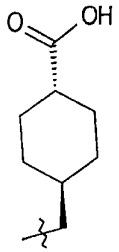
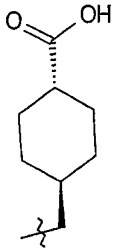
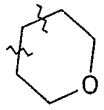
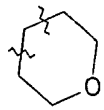
| Ex. No. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 258 | H |  |  |  | 2.65 | 451 | | B14 |
| 259 | H |  |  |  | 2.85 | 451 | | B14 |
| 260 | H |  |  |  | 2.37 | 453 | | B14 |

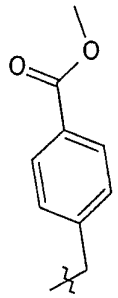
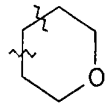
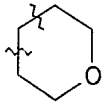
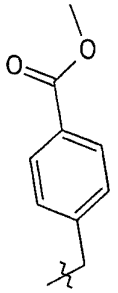
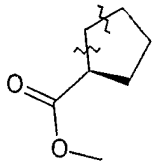
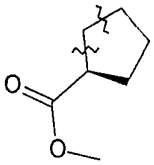
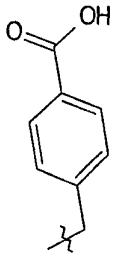
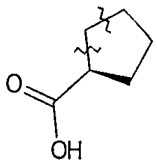
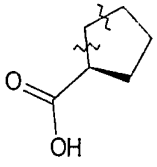
| Ex. No. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 261 | H |  |  | H | 2.37 | 433 | | B14 |
| 262 | H |  |  | H | 2.45 | 441 | | B14 |
| 263 | H |  |  | H | 2.34 | 433 | | B14 |

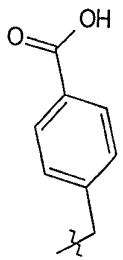
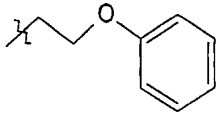
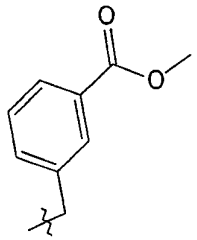
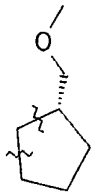
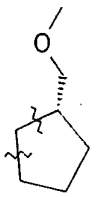
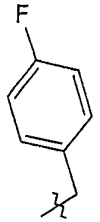
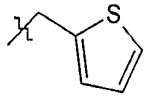
| Ex. No. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 264 | H |  |  |  | 2.30 | 445 | | B14 |
| 265 | H |  |  | H | 2.41 | 447 | | B14 |
| 266 | H |  |  | H | 2.45 | 447 | | B14 |

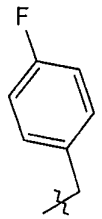
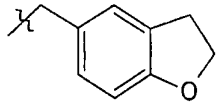
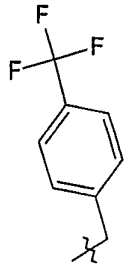
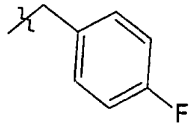
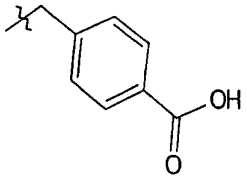
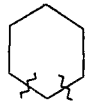
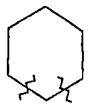
| Ex. No. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 267 | H |  |  |  | 2.48 | 455 | | B14 |
| 268 | H |  |  | H | 2.52 | 455 | | B14 |
| 269 | H |  |  |  | 2.45 | 459 | | B14 |

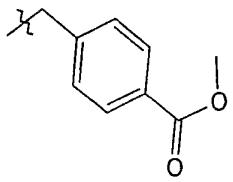
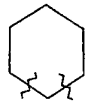
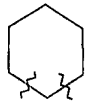
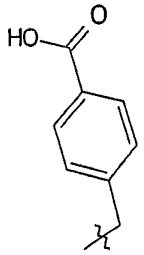
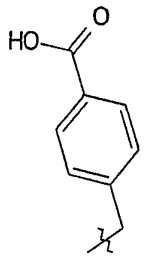
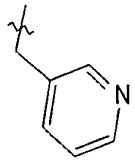
| Ex. No. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 270 | H |  |  |  | 2.48 | 459 | | B14 |
| 271 | H |  |  |  | 1.93 | 498 | | B14 |
| 272 | H |  |  |  | 2.63 | 520 | | B14 |

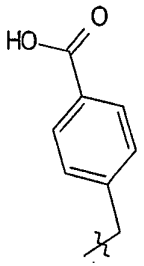
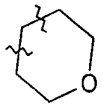
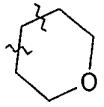
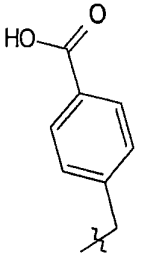
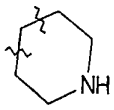
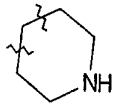
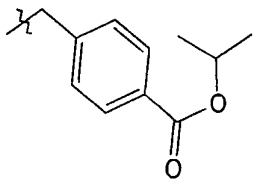
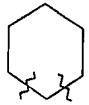
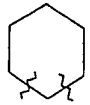
| Ex. No. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 273 | H |  |  |  | 2.78 | 548 | | B14 |
| 274 | H |  |  | H | 2.26 | 419 | | B14 |
| 275 | H |  |  |  | 2.3 | 431 | | B14 |

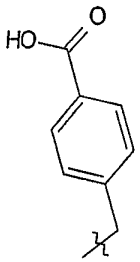
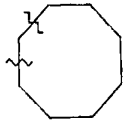
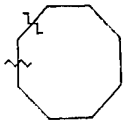
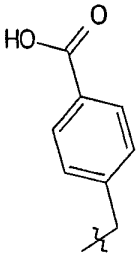
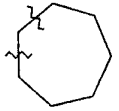
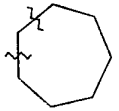
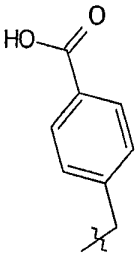
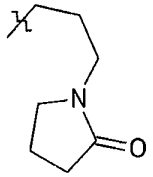
| Ex. No. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 276 | H |  |  |  | TLC (5% MeOH/95% CH2Cl2) Rf=0.10 | 439.3 | 185-237 | B1 |
| 277 | H |  |  |  | TLC ( 5% MeOH/95% CH2Cl2) Rf = 0.12 | 481.3 | 227 | B1 |
| 278 | H |  |  |  | TLC (2/4 MeOH/ CH2Cl2) Rf = 0.60 | 453.3 | decomp 260-295 | B1, C1 |

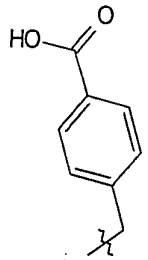
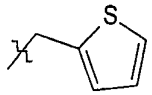
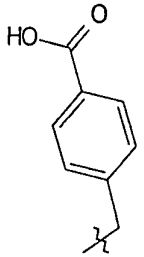
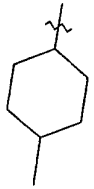
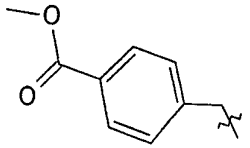
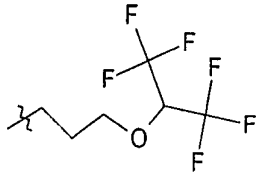
| Ex. No. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 279 |  |  |  |  | HPLC RT = 2.59 min | 475 | | B1 |
| 280 |  |  |  |  | TLC (90% EtOAc/10% MeOH) Rf = 0.22 | 467.5 | 122-124 | B1 |
| 281 |  |  |  |  | TLC (20% MeOH/80% EtOAc) Rf = 0.24 | 425.4 | 185-186 | B1 |

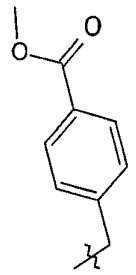
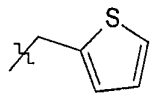
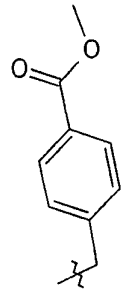
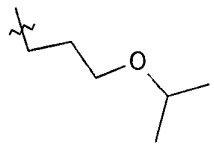
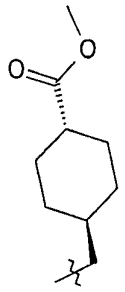
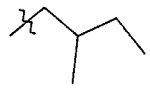
| Ex. No. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 282 | H |  |  | H | TLC (20% MeOH/80% EtOAc) Rf = 0.15 | 461.8 | 175-178 | B1 |
| 283 | H |  |  | H | TLC (20% MeOH/80% EtOAc) Rf = 0.22 | 487.3 | >210 | B1 |
| 284 | H |  |  |  | 1H NMR (DMSO) 4.65 ppm (2H, d, J = 5.7 Hz), 3.81/3.78 ppm (3H ea, 2 s) | 423 @ 2.99 min | >200 dec. | B2, B3 step 3 |

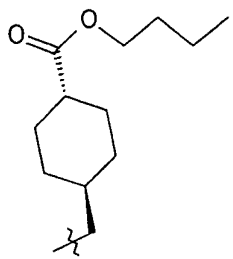
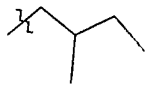
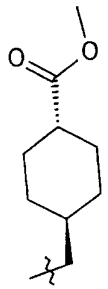
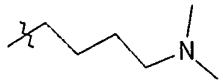
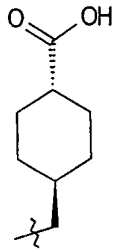
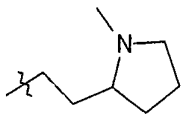
| Ex. No. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 285 | -H |  |  |  | 0.47 100% EtOAc | 437 @ 3.14 min | 180 | B2, B3 step 3 |
| 286 | -H |  |  |  | 0.04 33%MeOH/ EtOAc | 409 @ 2.94 min | >200 dec. | B2, B3 step 3 |
| 287 | -H |  |  | -H | 1H NMR (DMSO) 4.67ppm (2H, d, J = 5.74 Hz), 4.46ppm(2 H, d, J = 6.3 Hz) | 446 @ 2.47 min | >230 dec. | B2 step 1, D2 |

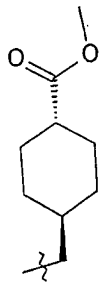
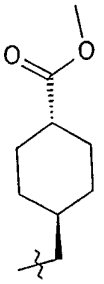
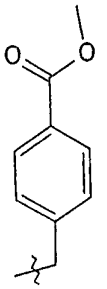
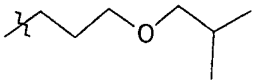
| Ex. No. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 288 |  |  |  |  | 0.16 33%MeOH/ EtOAc | 425 @ 2.03 min | >190 dec. | B2 |
| 289 |  |  |  |  | 1H NMR (DMSO) 4.82 ppm (2H, d, J = 4.5 Hz), 3.86 ppm (6H, s) | 424 @ 2.46 min | >210 dec. | B2 step 1, D2 |
| 290 |  |  |  |  | 0.63 100% EtOAc | 465 @ 2.22 min | | B2, C9 |

| Ex. No. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 291 | H |  |  |  | 1H NMR (DMSO) 4.80 ppm (2H, b s), 3.86 ppm (6H, s) | 451 @2.35 min | >250 dec. | B2 step 1, D2 |
| 292 | H |  |  |  | 1H NMR (DMSO) 4.80ppm (2H, d, J = 5.4 Hz), 3.85/3.87ppm (3 H ea, 2 s) | 437 @ 2.30 min | >280 dec. | B2 step 1, D2 |
| 293 | H |  |  | H | 1H NMR (DMSO) 4.81ppm (2H, d, J = 5.7 Hz), 3.84/3.87ppm (3 H ea, 2 s) | 480 @ 1.92 min | 250 | B2 step 1, D2 |

| Ex. No. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 294 | H |  |  | H | 0.80 33%MeOH/ EtOAc | 451 @ 2.22 | | B2 step 1, D2 |
| 295 | H |  |  | H | 1H NMR (DMSO) 4.73ppm (2H, m), 3.80/3.77ppm (3 H ea, 2 s) | 451 @ 2.47 min | | B2 step 1, B10 |
| 296 | H |  |  | H | TLC (1/1 EtOAc/ Hex) Rf = 0.67 | 577.4 | | A11, B1 |

| Ex. No. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 297 | H |  |  | H | TLC Rf = 0.37 (9/1 CH2Cl2/ MeOH) | 465.3 | | B1 |
| 298 | H |  |  | H | TLC Rf = 0.28 (9/1 CH2Cl2/MeOH) | 469.5 | | B1 |
| 299 | H |  |  | H | TLC Rf = 0.38 (100% EtOAc) | 445.6 | | B1 |

| Ex. No. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 300 | H |  |  | H | TLC Rf = 0.31 (100% EtOAc) | 487.6 | | B1 |
| 301 | H |  |  | H | HPLC RT = 2.40 (20-60% CH3CN/ H20) | 474.4 | | B1 |
| 302 | H |  |  | H | HPLC RT=1.02 (20-70% CH3CN/ H20) | 472.5 | | B1 |

| Ex. No. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 303 | H |  |  |  | HPLC RT=2.87 (20-80% CH3CN/ H20) | 429.5 | | B1 |
| 304 | H |  |  |  | HPLC RT=2.56 (20-60% CH3CN/ H20) | 403.4 | | B1 |
| 305 | H |  |  |  | TLC Rf = 0.18 (100% EtOAc) | 497.3 | | B1 |

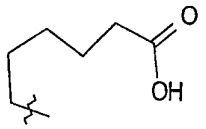
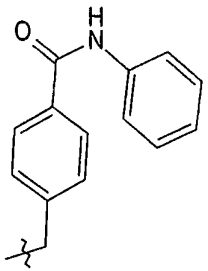
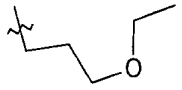
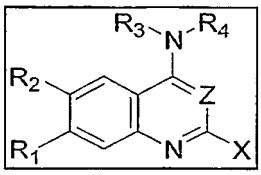
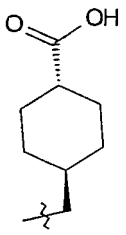
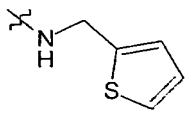
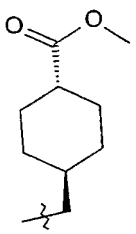
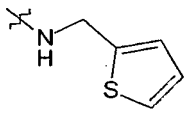
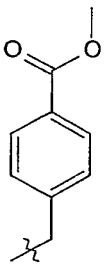
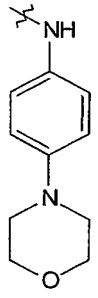
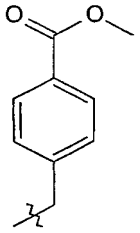
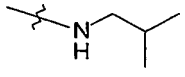
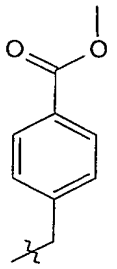
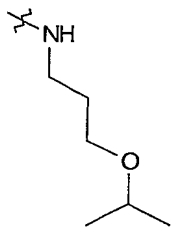
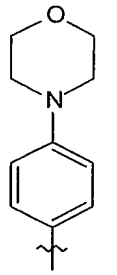
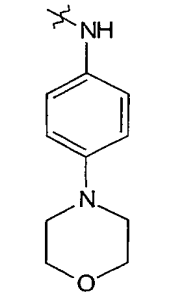
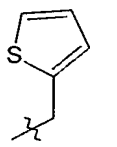
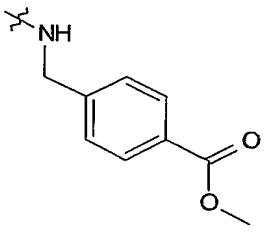
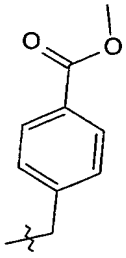
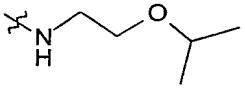
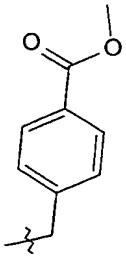
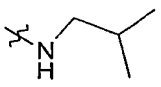
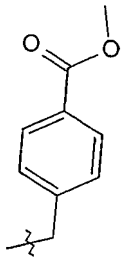
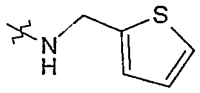
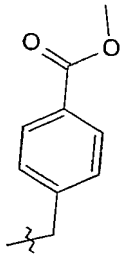
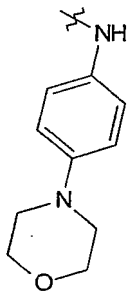
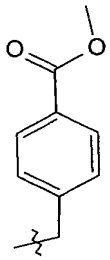
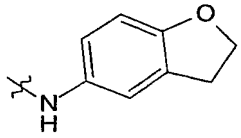
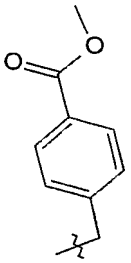
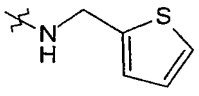
| Ex. No. | $R_3$ | $R_4$ | $R_5$ | $R_6$ | TLC/HPLC | MS (MH+) | mp | Prep Method |
|---|---|---|---|---|---|---|---|---|
| 306 |  |  |  |  | | | | B14 |
| 307 |  |  |  |  | TLC Rf = 0.29 (20% 80% CHCl3) | 516.4 | 174-175 | B1, C1, C2 |

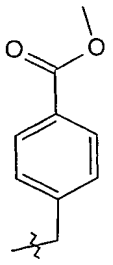
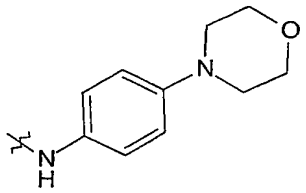
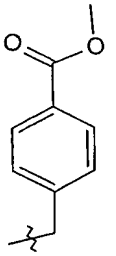
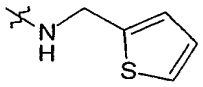
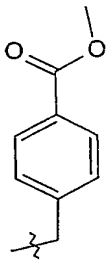
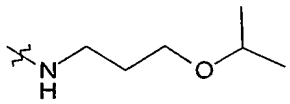
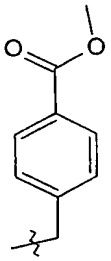
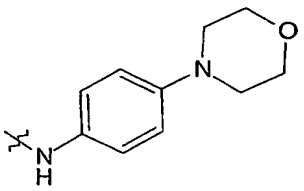
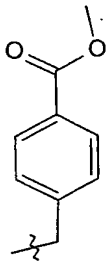
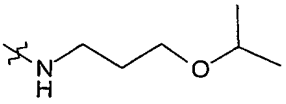
**Table 3. Miscellaneous Quinazolines and Quinolines**

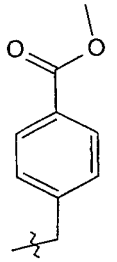
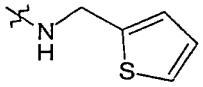
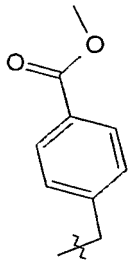
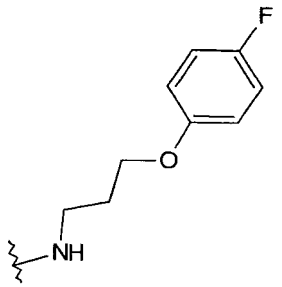
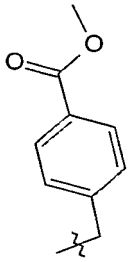
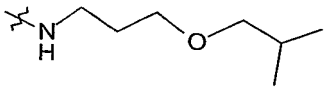
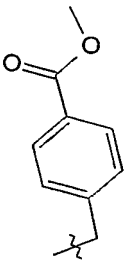
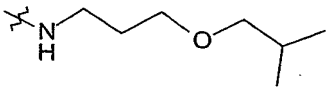


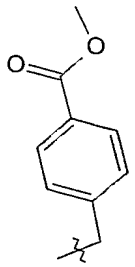
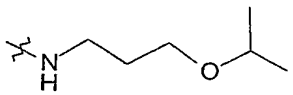
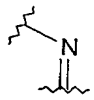
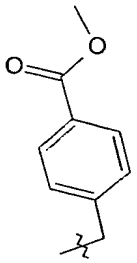
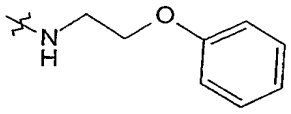
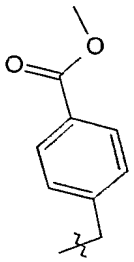
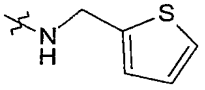
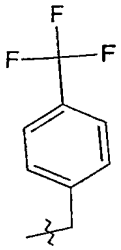
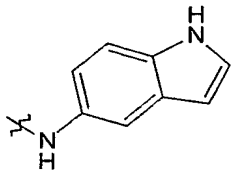
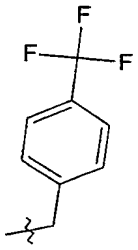
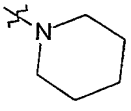
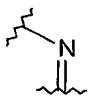
| Ex. | $R_1$ | $R_2$ | $R_3$ | $R_4$ | X | Z |
|---|---|---|---|---|---|---|
| 308 | H | H | H |  |  |  |
| 309 | H | H | H |  |  |  |
| 310 | Cl | H | H |  |  |  |
| 311 | Cl | H | H |  |  |  |

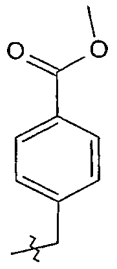
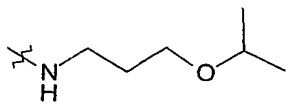
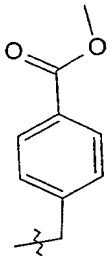
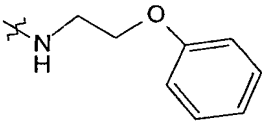
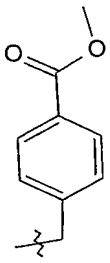
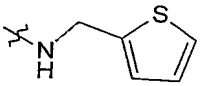
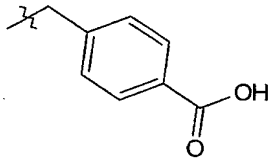
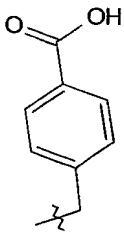
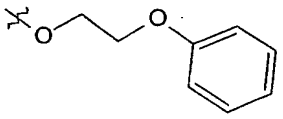
| Ex. | $R_1$ | $R_2$ | $R_3$ | $R_4$ | X | Z |
|---|---|---|---|---|---|---|
| 312 |  |  |  |  |  |  |
| 313 |  |  |  |  |  |  |
| 314 |  |  |  |  |  |  |
| 315 |  |  |  |  |  |  |
| 316 |  |  |  |  |  |  |

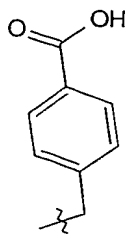
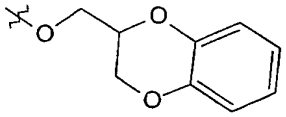
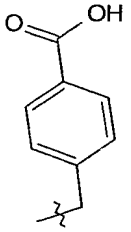
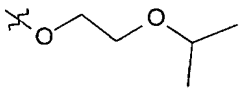
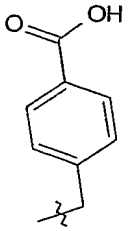
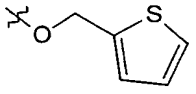
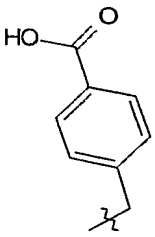
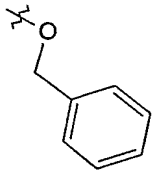
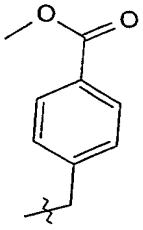
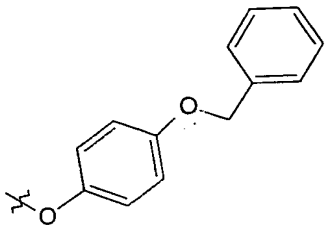
| Ex. | $R_1$ | $R_2$ | $R_3$ | $R_4$ | X | Z |
|---|---|---|---|---|---|---|
| 317 | H | H | H |  |  |  |
| 318 | H | H | H |  |  |  |
| 319 |  | H | H |  |  |  |
| 320 |  | H | H |  |  |  |

| Ex. | $R_1$ | $R_2$ | $R_3$ | $R_4$ | X | Z |
|---|---|---|---|---|---|---|
| 321 | H | F | H |  |  |  |
| 322 | H | F | H |  |  |  |
| 323 | H | F | H |  |  |  |
| 324 | H | Br | H |  |  |  |
| 325 | H | Br | H |  |  |  |

| Ex. | $R_1$ | $R_2$ | $R_3$ | $R_4$ | X | Z |
|---|---|---|---|---|---|---|
| 326 | H | Br | H |  |  |  |
| 327 | H | Br | H |  |  |  |
| 328 | H | Br | H |  |  |  |
| 329 | H | O | H |  |  |  |

| Ex. | $R_1$ | $R_2$ | $R_3$ | $R_4$ | X | Z |
|---|---|---|---|---|---|---|
| 330 | H | O | H |  |  |  |
| 331 | H | O | H |  |  |  |
| 332 | H | O | H |  |  |  |
| 333 | H | Br | H |  |  |  |
| 334 | H | Br | H |  |  |  |

| Ex. | $R_1$ | $R_2$ | $R_3$ | $R_4$ | X | Z |
|---|---|---|---|---|---|---|
| 335 | H | I | H |  |  |  |
| 336 | H | I | H |  |  |  |
| 337 | H | I | H |  |  |  |
| 338 | H | Cl | H |  |  |  |
| 339 | H | Cl | H |  |  |  |

| Ex. | $R_1$ | $R_2$ | $R_3$ | $R_4$ | X | Z |
|---|---|---|---|---|---|---|
| 340 | H | Cl | H |  |  |  |
| 341 | H | Cl | H |  |  |  |
| 342 | H | Cl | H |  |  |  |
| 343 | H | Cl | H |  |  |  |
| 344 | H | Cl | H |  |  |  |

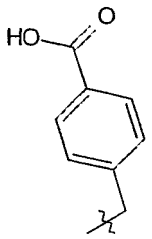
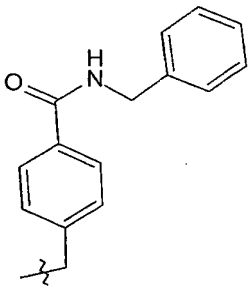
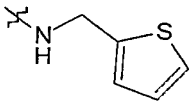
| Ex. | $R_1$ | $R_2$ | $R_3$ | $R_4$ | X | Z |
|---|---|---|---|---|---|---|
| 345 |  |  |  |  |  |  |
| 346 |  |  |  |  |  |  |

**Table 4. Analytical Data for Table 3 Examples**

| Example No. | TLC/HPLC | MS (MH+) | mp | Prep Method |
|---|---|---|---|---|
| 308 | 2.41 | 397 | | A8, B1 |
| 309 | 2.73 | 411 | | A8, B1 |
| 310 | HPLC RT (90:10 - 10:90 H2O/CH3CN) 1.99 MIN. 90% PURITY | 504.5 | | A7, B1 step 1, B11 |
| 311 | HPLC RT (90:10 - 10:90 H2O/CH3CN) 2.28 MIN | 399.4 | 132-135 | A7, B1 step 1, B11 |
| 312 | HPLC RT (90:10 - 10:90 H2O/CH3CN) 2.19 MIN. | 443.4 | 66-72 | A7, B1 step 1, B11 |
| 313 | TLC Rf (100% EtOAc) 0.82 | 517.3 | 209-213 | A7, B12 |
| 314 | TLC Rf (90:10 CH2Cl2/MeOH) 0.75 | 439.3 | 91-97 | A7, B13 |
| 315 | | 409.4 | | A8, B1 |
| 316 | | 365.4 | | A8, B1 |
| 317 | | 405.3 | | A8, B1 |
| 318 | | 470.3 | | A8, B1 |
| 319 | TLC Rf = 0.54 (100% EtOAc) | 457.2 | | A1, B1 |
| 320 | TLC Rf = 0.14 (100% EtOAc) | 435.1 | | A1, B1 |
| 321 | TLC Rf = 0.66 (3/2 Hex/EtOAc) | 488 | | A2, B1 |
| 322 | TLC R F= 0.68(3/2 Hex/EtOAc) | 423 | | A2, B1 |
| 323 | TLC Rf=0.64 (3/2 Hex/EtOAc) | 427 | | A2, B1 |
| 324 | TLC RT = 0.60 (100% EtOAc) | 458.5 | | A2, A8, B1 |
| 325 | TLC Rf = 0.40 (100% EtOAc) | 487.4 | | A2, A8, B1 |
| 326 | TLC Rf = 0.73 (100% EtOAc) | 483.4 | | A2, A8, B1 |
| 327 | TLC Rf = 0.40 (4/1 EtOAc/Hex) | 539.4 | | A2, A8, A9, B1 |
| 328 | TLC Rf = 0.19 (1/1 Hex/EtOAc) | 501.5 | | A2, A8, B1 |
| 329 | TLC Rf = 0.16 (95/5 CH2Cl2/MeOH) | 453.5 | | A5, B1 |
| 330 | TLC Rf = 0.31 (9/1 CH2Cl2/MeOH) | 439.4 | | A5, B1 |

| Example No. | TLC/HPLC | MS (MH+) | mp | Prep Method |
|---|---|---|---|---|
| 331 | TLC Rf = 0.31 (9/1 CH2Cl2/MeOH) | 459.4 | | A5, B1 |
| 332 | TLC Rf=0.38 (9/1 CH2Cl2/MeOH) | 435.3 | | A5, B1 |
| 333 | TLC Rf = 0.28 (1/1 Hex/EtOAc) | 512.4 | | A2, A8, B1 |
| 334 | TLC Rf = 0.77 (1/1 Hex/EtOAc) | 465.2 | | A2, A8, B1 |
| 335 | TLC Rf =0.12 (1/1 Hex/EtOAc) | 535.3 | | A3, A8, B1 |
| 336 | TLC Rf=0.23 (1/1 Hex/EtOAc) | 555.2 | | A3, A8, B1 |
| 337 | TLC Rf = 0.27 (1/1 Hex/EtOAc) | 531.1 | | A3, A8, B1 |
| 338 | 0.18 30%MeOH/EtOAc | 344 @ 2.72 min | | A6,B9, B2 step 2, B3, step 3 |
| 339 | 0.50 20%MeOH/DCM | 450 @ 2.34 min | | A6, B2 step 1, D3 |
| 340 | 0.51 20%MeOH/DCM | 478 @ 2.39 | | A6, B2 step 1, D3 |
| 341 | 0.40 20%MeOH/DCM | 416 @ 2.07 min | | A6, B2 step 1, D3 |
| 342 | 0.35 20%MeOH/DCM | 426 @ 2.29 | | A6, B2 step 1, D3 |
| 343 | 0.40 25%MeOH/DCM | 420 @ 2.29 min | | A6, B2 step 1, D3 |
| 344 | TLC (1/1 EtOAc/Hex) Rf = 0.83 | 526.3 | 93-94 | A6, B1 step 1, D4 |
| 345 | TLC Rf = 0.17 (9/1 CH2Cl2/MeOH) | 370.3 | | |
| 346 | TLC Rf (100 EtOAc) 0.64 | 514.4 | 115-117 | D7, C2 |

***Description of Inhibiting Prolyl Peptidase, Inducing Apoptosis and Treatment of Cancer***

Apoptosis (programmed cell death) is an essential process in the development and maintenance of homeostasis in an organism (1). The growth fraction of a tumor is governed by the rate of cellular division as well as the rate of cell death: if the rate of division exceeds that of cell death, then net tumor expansion occurs. Importantly, net growth rates of tumors do not generally correlate directly with the rate of cell division within the tumor, as assessed by the abundance of mitotic figures. Hence, aberrant apoptotic rate plays an important role in tumor growth and expansion (2, 3).

Studies have demonstrated that cells transfected with either *myc* or *ras* oncogenes exhibit altered proliferation and apoptotic rates (4, 5). Transfectant cell lines that displayed elevated rates of *both* cell division and apoptosis lead to established tumors with reduced efficiency, compared to transfectant lines that displayed an elevated rate of cell division and reduced rate of apoptosis. Moreover, tumors with comparable mitotic indices exhibit radically different net growth rates depending on whether the basal apoptotic rates are low (yielding high tumor growth rates) or high (yielding low tumor growth rates). For example, low apoptotic rates are thought to drive the observed net growth rates observed in prostate cancer (6). Hence, targets that regulate apoptotic pathways in tumor cells should provide important points for novel therapeutic intervention and, should lead to an improved therapeutic effect (7).

Proteases are attractive cancer drug targets since they are known to regulate apoptotic signal transduction (8, 9). For example, work on apoptosis initiated by specific inhibitors of the proteasome complex has been reported in the literature, where lactacystin and other proteasome inhibitors are shown to cause apoptosis in a number of cell lines (10, 11).

Recent publications have identified prolylpeptidase (QPP) as an intracellular protease involved in the repression of apoptosis and, as such, prolylpeptidase is thought to be an anti-apoptotic factor (12, 13). Prolylpeptidase is a serine protease that is irreversibly inactivated by diispropyl-fluorophosphate (DFP) through covalent modification of Ser154 (12) and unpublished data. It is the only known human serine protease that is fully active without additional post-translational removal of inhibitory peptide. In addition, the enzyme is localized to novel non-lysosomal cytosolic vesicles (14). Recombinant prolylpeptidase as

well as prolylpeptidase purified from natural sources are active as dimeric proteins (106 kDa), based on size exclusion chromatography, although the gene encodes a putative enzyme with a predicted mass of 58 kDa (15).

Active prolylpeptidase has been identified in a number of solid tumor cell lines of different histological types including those from colon (HCT116 and DLD1), prostate (PC3), and breast (MDA-MB-435). In addition, expression data for prolylpeptidase mRNA shows a very limited distribution across adult human tissues, with highest levels observed in the testis, and moderate levels in prostate, skeletal muscle and brain. Increased expression of prolylpeptidase mRNA in human tumor specimens and the published biological data on the enzyme suggest that prolylpeptidase plays an important role in tumor cell growth or survival. In summary, these data suggest that selective inhibition of prolylpeptidase activity in tumor cells could lead to increased apoptotic rates and growth inhibition.

Described below are the results of prolylpeptidase inhibition assays and apoptosis induction assays which show the effect of the applicants described compounds.
The prolylpeptidase enzyme used in the prolylpeptidase assay protocol cited below was described by Kapeller-Libermann et al. (U.S. Serial No. 09/345,469, the contents of which is hereby incorporated by reference; see also WO 01/00812).

**Prolylpeptidase Assay Protocol**

Test compounds were diluted serially 1:5 in 5% DMSO/95% water and 5 µL was added to give 100 µL as a final volume to a well containing prolylpeptidase enzyme in buffer. Drug had a final concentration ranging from 10 µM to 0.12 µM. The Ala-Pro-AFC dipeptide substrate (AFC is 7-amino-4-trifluoro-methylcoumarin) in MTEN buffer was used at a final concentration of 200 µL and the reaction was initiated with 10 nM final concentration of recombinant prolylpeptidase. The reaction was allowed to proceed for 20 min at room temperature and quenched with 20 µL of 1 M Glycine-HCl pH 2.5. The 96 well plates were read as an endpoint assay at an excitation of 400 nm and emission of 505 nm. The final DMSO concentration was 0.25% in the assay.

Ala-Pro-AFC is a dipeptide substrate with a conjugated AFC fluorophore at the C-terminus. Hydrolysis of the dipeptide substrate releases free AFC which is excited at 400 nm and emission of 505 nm in a spectrofluorometer.

Assay buffer is 50 mM MTEN Buffer pH 4.5 (50 mM MES, 25 mM Tris, 25 mM ethanolamine, 100 mM NaCl). Enzyme storage buffer was 50 mM Tris pH 7.0, 50% glycerol and was stored at -80 °C. It was diluted in assay buffer just prior to initiation of the assay.

All example compounds of formula (I) and (II) were tested in the above prolylpeptidase assay and were found to inhibit prolylpeptidase at or below a concentration of 10 μM, except for examples 245, 305 and 307.

**Multiparameter Apoptosis Assay**

The induction of apoptosis by prolylpeptidase inhibitors was measured in whole cells using the multiparameter apoptosis assay (MPA). The assay uses the ArrayScan II (Cellomics Inc. Pittsburgh, PA) and the MPA application software to simultaneously measure three parameters of apoptosis 1.) nuclear fragmentation 2.) actin content and 3.) mitochondrial potential. Test compounds were dissolved in 100% DMSO and diluted serially 1:2 in DMEM with 10% fetal calf serum (final DMSO concentration 0.25%) and added to HCT-116 cells growing in 96-well tissue culture plates. The final drug concentrations ranged from 25 μM to 0.39 μM. Cells were exposed to compound for either one or 24 hours depending on the experiment. The MPA assay was run according to the manufactures' protocol. The % of control for each compound concentration is determined using the formula; %Control = (((Experimental Units)-Blank Units)/Units from untreated Control-Blank Units)*100. A curve is fitted and a value for Y=50% ($IC_{50}$) using the formula Y=A+((B-A)/(1+(((B-E)(X/C)^D)/(E-A))). The average of the $IC_{50}$ values for nuclear fragmentation, actin content and mitochondria index is used as the MPA $IC_{50}$.

Certain exemplary compounds of formulae (I) and (II) were tested in the above apoptosis assay and were found to induce apoptosis at or below a concentration of 25 μM. Compounds 12, 24, 32, 44, 46, 48, 49, 54, 59, 61, 62, 64, 65, 67, 68, 70, 77, 79, 81, 98, 127,

130, 179, 186, 219, 222, 229, 235, 236, 242, 243, 245, 256, 281-283, 296-298, 300, 307, 318, 319 and 327-333 were found to induce apoptosis at or below a concentration of 10 μM.

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(All references are hereby incorporated by reference)

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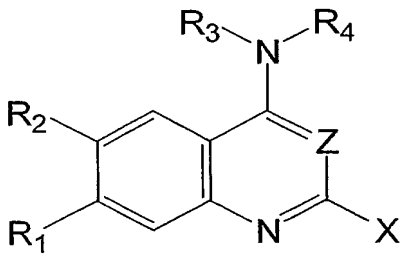
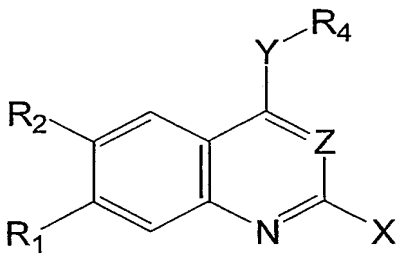
Other embodiments of the invention will be apparent to the skilled in the art from a consideration of this specification or practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with the scope and spirit of the invention being indicated by the following claims.

What is claimed is:

1. A compound of the formula:




or




(I) (II)

wherein

Z is CH or N;

Y is O or S;

X is $OR_5$ or $NR_5R_6$;

$R_1$ and $R_2$ are independently selected from the group consisting of hydrogen, amino, cyano, halogen, hydroxy and nitro,

wherein $R_1$ and $R_2$ are both not hydrogen;

$R_3$ is selected from the group consisting of:

(a) hydrogen, and

(b) -($C_1$-$C_{10}$) linear or branched alkyl;

$R_4$ is -$(CH_2)_y$-$R_4$' wherein:

$R_4$' is selected from the group consisting of:

(a) -($C_1$-$C_5$) linear or branched alkyl optionally substituted with one to three substituents selected from the group consisting of:

(1) cyano,

(2) halogen,

(3) hydroxy,

(4) nitro,

(5) -($C_1$-$C_5$) linear or branched alkyl optionally substituted by halogen,

(6) -($C_1$-$C_5$) alkoxy-,

(7) -C(=O)$R_7$,

(8) -C(=O)O$R_7$,

(9) -C(=O)N$R_8R_9$,

(10) -S(=O)$R_{10}$, and

(11) -S(=O)$_2R_{10}$;

(b) -($C_3$-$C_8$) cycloalkyl,

(c) -($C_6$-$C_{10}$) aryl,

wherein (b) and (c) are optionally substituted with one to three substituents selected from the group consisting of

(1) amino,

(2) cyano,

(3) halogen,

(4) hydroxy,

(5) nitro,

(6) oxo,

(7) -($C_1$-$C_5$) linear or branched alkyl optionally substituted by halogen or hydroxy,

(8) -($C_1$-$C_5$) haloalkoxy-,

(9) -$(CH_2)_n$C(=O)$R_7$,

(10) -$(CH_2)_n$C(=O)O$R_7$,

(11) -$(CH_2)_n$C(=O)C(=O)-O$R_7$,

(12) -$(CH_2)_n$C(=O)N$R_8R_9$,

(13) -S(=O)$R_{10}$,

(14) -S(=O)$_2R_{10}$,

(15) -C(=N-$R_{10}$)-($C_1$-$C_5$)-alkyl, and

(16) a saturated or unsaturated four to six membered heterocyclic ring containing one to four heteroatoms selected from the

from the group consisting of nitrogen, oxygen and sulfur, wherein said ring contains at least one carbon atom;

and

(d) a saturated or fully unsaturared four to six membered heterocyclic ring containing one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring contains at least one carbon atom and wherein said ring is optionally substituted with one to three substituents selected from the group consisting of amino, cyano, halogen, hydroxy, nitro, oxo, ($C_1$-$C_5$)-alkoxy, -$(CH_2)_nC(=O)OR_7$, -$(CH_2)_nC(=O)NR_8R_9$, -$S(=O)R_{10}$, -$S(=O)_2R_{10}$ and -($C_1$-$C_5$) linear or branched alkyl optionally substituted by halogen,

or

$R_3$ and $R_4$ form, together with the nitrogen to which they are attached, a saturated or fully unsaturated four to eight membered heterocyclic ring, wherein the nitrogen is the only heteroatom, which is optionally substituted with one to three substituents selected from the group consisting of amino, cyano, halogen, hydroxy, nitro, oxo, -($C_1$-$C_5$) alkoxy-, phenyl, -$C(=O)R_7$, -$(CH_2)_nC(=O)OR_7$, -$(CH_2)_nC(=O)NR_8R_9$, -$S(=O)R_{10}$, -$S(=O)_2R_{10}$ and -($C_1$-$C_5$) linear or branched alkyl optionally substituted by halogen;

$R_5$ has the formula -$(CHR_{11})_m$-A or -$(CHR_{11})_p$-O-A, where A is selected from the group consisting of:

(a) hydrogen,

(b) -($C_1$-$C_5$) linear or branched alkyl optionally substituted with cyano, halogen, hydroxy, -($C_1$-$C_5$) alkoxy- or -$NR_8R_9$,

(c) -($C_3$-$C_8$) cycloalkyl optionally substituted with cyano, halogen, hydroxy, -($C_1$-$C_5$) -alkyl, -($C_1$-$C_5$) alkoxy- or -$NR_8R_9$,

(d) -($C_6$-$C_{10}$) aryl optionally substituted with one to three substituents selected from the group consisting of:

(1) cyano,

(2) halogen,

(3) hydroxy,

(4) nitro,

(5) $-NR_8R_9$,

(6) $-(C_1-C_5)$ linear or branched alkyl optionally substituted with $-NR_8R_9$ or halogen,

(7) $-(C_1-C_5)$-alkoxy wherein the alkyl is optionally substituted with $-NR_8R_9$ or halogen,

(8) $-(C_6-C_{10})$ aryl-$(C_1-C_5)$-alkoxy-

(9) $-(C_6-C_{10})$ aryloxy optionally substituted with halogen,

(10) $-(C_6-C_{10})$ -aryl optionally substituted with halogen,

(11) $-CH_2-(C_6-C_{10})$-aryl,

(12) $-C(=O)R_7$,

(13) $-C(=O)OR_7$,

(14) $-C(=O)NR_8R_9$,

(15) $-S(=O)R_{10}$,

(16) $-S(=O)_2R_{10}$, and

(17) a saturated or fully unsaturated four to eight membered heterocyclic ring containing one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring:

(a17) contains at least one carbon atom,

(b17) is directly linked to the $-(C_6-C_{10})$-aryl or is linked to the $-(C_6-C_{10})$-aryl via an -O- linkage, and

(c17) is optionally substituted with $-(C_1-C_5)$-alkyl, $-(CH_2)_nC(=O)OR_7$ or $-(CH_2)_nC(=O)NR_8R_9$,

(e) a saturated or fully unsaturated four to eight membered heterocyclic ring containing one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring contains at least one carbon atom, and is optionally substituted with

(1) -($C_1$-$C_5$)-alkyl optionally substituted by halogen,
(2) phenyl optionally substituted by halogen,
(3) -($C_1$-$C_5$)-alkoxy- wherein the alkyl is optionally substituted with halogen,
(4) -($C_6$-$C_{10}$) aryloxy wherein the aryl is optionally substituted with halogen, or
(5) oxo,

and

(f) a fused bicyclo ring wherein one ring is a saturated or fully unsaturated five to six membered heterocyclic ring which contains one to three heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said heterocyclic ring contains at least one carbon atom, and the other ring is a saturated or fully unsaturated five to eight membered carbocycle,

$R_6$ is selected from the group consisting of:

(a) hydrogen, and
(b) -($C_1$-$C_5$) linear or branched alkyl,

wherein $R_5$ and $R_6$ are not both hydrogen;

or

$R_5$ and $R_6$ form, together with the nitrogen to which they are attached, a saturated or fully unsaturated four to eight membered heterocyclic ring, which optionally contains one to three additional nitrogen atoms wherein said ring contains at least one carbon atom, and wherein said ring is optionally substituted with one to three substituents selected from the group consisting of:

(a) amino,
(b) cyano,
(c) halogen,
(d) hydroxy,
(e) nitro,

(f) oxo,

(g) -($C_1$-$C_5$) linear or branched alkyl optionally substituted by halogen or -($C_1$-$C_5$) -alkoxy,

(h) -($C_1$-$C_5$) alkoxy,

(i) -($C_1$-$C_5$) alkoxy-($C_1$-$C_5$)-alkyl,

(j) -($C_6$-$C_{10}$) aryl optionally substituted by halogen or -($C_1$-$C_5$)-alkyl,

(k) -($C_1$-$C_5$)-alkyl-phenyl optionally substituted by halogen or -($C_1$-$C_5$)-alkyl,

(l) -$(CH_2)_nC(=O)OR_7$,

(m) -$(CH_2)_nC(=O)NR_8R_9$,

(n) -$(CH_2)_nNR_8R_9$,

(o) -$S(=O)R_{10}$,

(p) -$S(=O)_2R_{10}$, and

(q) -$(CH_2)_n$-Q, wherein Q is a saturated or fully unsaturated four to eight membered heterocyclic ring containing one to four nitrogens, wherein said ring contains at least one carbon atom;

wherein ($R_3$ and $R_4$) ≠ ($R_5$ and $R_6$) when:

(1) $R_3/R_4$ or $R_5/R_6$ contain an unsubstituted -$(CH_2)_n$-$C_6$-$C_{10}$-aryl substituent, or

(2) $R_3/R_4$ or $R_5/R_6$ form a heterocyclic ring;

$R_7$ is selected from the group consisting of hydrogen, -($C_1$-$C_5$) linear or branched alkyl, phenyl, -($C_1$-$C_5$)-alkyl-phenyl, and -($C_3$-$C_8$) cycloalkyl which are optionally substituted with one to three substituents selected from the group consisting of halogen, oxo, -($C_1$-$C_5$) alkoxy, -$C(=O)R_{11}$ and -($C_1$-$C_5$) linear or branched alkyl optionally substituted by halogen;

$R_8$ and $R_9$ are independently selected from the group consisting of:

(a) hydrogen,

(b) -($C_1$-$C_5$) linear or branched alkyl which is optionally substituted with a substituent selected from the group consisting of halogen and -($C_1$-$C_5$) alkoxy,

(c) -($C_1$-$C_5$) alkoxy,

(d) -($C_6$-$C_{10}$) aryl, and

(e) -$(CH_2)_n$-R wherein R is a five to six membered saturated or fully unsaturated heterocyclic ring containing one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring contains at least one carbon atom,

wherein (c)-(e) are optionally substituted with one to three substituents selected from the group consisting of halogen, -($C_1$-$C_5$) alkoxy, -C(=O)$R_7$ and -($C_1$-$C_5$) linear or branched alkyl optionally substituted by halogen,

or

$R_8$ and $R_9$ form, together with the nitrogen to which they are attached, a saturated or fully unsaturated four to eight membered heterocyclic ring, optionally containing one to three additional heteroatoms selected from the group consisting of nitrogen and oxygen wherein said ring contains at least one carbon atom and wherein said heterocyclic ring is optionally substituted with -($C_1$-$C_5$) linear or branched alkyl;

$R_{10}$ is hydrogen, -$NR_8R_9$, -$OR_{11}$, -($C_1$-$C_5$) linear or branched alkyl, or phenyl;

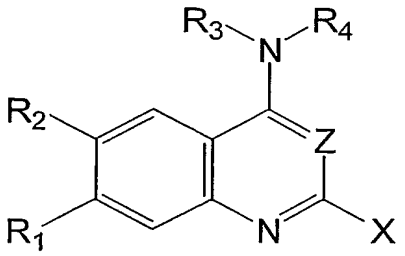
each occurrence of $R_{11}$ is independently selected from the group consisting of hydrogen, -($C_1$-$C_5$) linear or branched alkyl and phenyl;

n, m and p are independently an integer from 0 - 3;

y is an integer from 0 - 2;

or a purified stereoisomer or stereoisomer mixture of said compound or a salt of said compound or purified stereoisomer or stereoisomer mixture thereof.

2. A compound of the formula:

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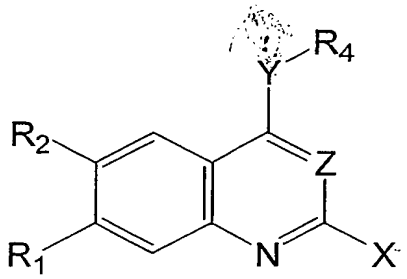



(I) (II)

wherein

Z is CH or N;

Y is O or S;

X is $OR_5$ or $NR_5R_6$;

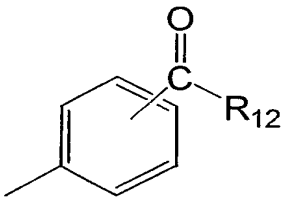
$R_1$ and $R_2$ are hydrogen;

$R_3$ is selected from the group consisting of:

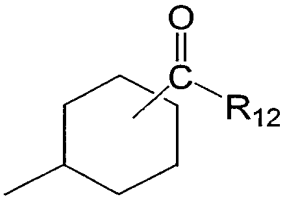
(a) hydrogen, and

(b) -($C_1$-$C_5$) linear or branched alkyl;

$R_4$ is -$(CH_2)_yR_4'$, wherein




or




;

$R_4'$ is:

$R_5$ has the formula -$(CHR_{11})_m$-A or -$(CHR_{11})_p$-O-A, where A is selected from the group consisting of:

(a) hydrogen,

(b) -($C_1$-$C_5$) linear or branched alkyl optionally substituted with cyano, halogen, hydroxy, -($C_1$-$C_5$) alkoxy or -$NR_8R_9$,

(c) -($C_3$-$C_8$) cycloalkyl optionally substituted with cyano, halogen, hydroxy, -($C_1$-$C_5$)-alkyl, -($C_1$-$C_5$) alkoxy or -$NR_8R_9$,

(d) -($C_6$-$C_{10}$) aryl optionally substituted with one to three substituents selected from the group consisting of:

(1) cyano,

(2) halogen,

(3) hydroxy,

(4) nitro,

(5) $-NR_8R_9$,

(6) $-(C_1-C_5)$-alkyl optionally substituted with halogen,

(7) $-(C_1-C_5)$-alkoxy wherein the alkyl is optionally substituted $-NR_8R_9$ or halogen,

(8) $-(C_6-C_{10})$-aryl-$(C_1-C_5)$-alkoxy

(9) $-(C_6-C_{10})$-aryloxy optionally substituted with halogen

(10) $-(C_6-C_{10})$-aryl optionally substituted with halogen,

(11) $-CH_2-(C_6-C_{10})$-aryl,

(12) $-C(=O)R_7$,

(13) $-C(=O)OR_7$,

(14) $-C(=O)NR_8R_9$,

(15) $-S(=O)R_{10}$;

(16) $-S(=O)_2R_{10}$; and

(17) a saturated or fully unsaturated four to eight membered heterocyclic ring containing one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring:

(a17) contains at least one carbon atom;

(b17) is directly linked to the $-(C_6-C_{10})$-aryl or is linked to the $-(C_6-C_{10})$-aryl via an -O- linkage; and

(c17) is optionally substituted with $-(C_1-C_5)$-alkyl, $-(CH_2)_nCOOR_7$ or $-(CH_2)_nCONR_8R_9$,

and

(e) a saturated or fully unsaturated four to eight membered heterocyclic ring containing one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring contains at least one carbon atom, and is optionally substituted with

(1) -($C_1$-$C_5$)-alkyl optionally substituted by halogen,
(2) phenyl optionally substituted by halogen,
(3) -($C_1$-$C_5$)-alkoxy- wherein the alkyl is optionally substituted with halogen,
(4) -($C_1$-$C_5$)-aryloxy- wherein the aryl is optionally substituted with halogen, or
(5) oxo;

$R_6$ is selected from the group consisting of:
(a) hydrogen, and
(b) -($C_1$-$C_5$) linear or branched alkyl,

wherein $R_5$ and $R_6$ are not both hydrogen;

$R_5$ and $R_6$ form, together with the nitrogen to which they are attached, a saturated or fully unsaturated four to eight membered heterocyclic ring, optionally containing one to three additional heteroatoms selected from the group consisting of nitrogen and oxygen wherein said ring contains at least one carbon atom wherein said heterocyclic ring is optionally substituted with -($C_1$-$C_5$) alkyl;

$R_7$ is selected from the group consisting of hydrogen, -($C_1$-$C_5$) linear or branched alkyl, phenyl, -($C_1$-$C_5$)-alkyl-phenyl, and -($C_3$-$C_8$) cycloalkyl which are optionally substituted with one to three substituents selected from the group consisting of halogen, oxo, -($C_1$-$C_5$) alkoxy-, -C(=O)$R_7$ and -($C_1$-$C_5$) linear or branched alkyl optionally substituted by halogen;

$R_8$ and $R_9$ are independently selected from the group consisting of:
(a) hydrogen,
(b) -($C_1$-$C_5$) linear or branched alkyl, which is optionally substituted with a substituent selected from the group consisting of halogen and -($C_1$-$C_5$) alkoxy,
(c) -($C_1$-$C_5$) alkoxy,
(d) -($C_6$-$C_{10}$) aryl, and

(e) $-(CH_2)_n-R$ wherein R is a saturated or fully unsaturated five to six membered heterocyclic ring containing one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring contains at least one carbon atom,

wherein (c)-(e) are optionally substituted with one to three substituents selected from the group consisting of halogen, $-(C_1-C_5)$ alkoxy- and $-(C_1-C_5)$ linear or branched alkyl optionally substituted by halogen;

$R_{10}$ is hydrogen, $-NR_8R_9$, $-OR_{11}$, $-(C_1-C_5)$ linear or branched alkyl, or phenyl;

each occurrence of $R_{11}$ is independently selected from the group consisting of hydrogen, $-(C_1-C_5)$ linear or branched alkyl and phenyl;

$R_{12}$ is $-R_{13}$, $-OR_{13}$, or $-NR_{14}R_{15}$;

$R_{13}$ is

(a) hydrogen,

(b) $-(C_1-C_5)$ linear or branched alkyl optionally substituted with halogen, or

(c) phenyl optionally substituted with halogen;

$R_{14}$ and $R_{15}$ are independently selected from the group consisting of:

(a) hydrogen,

(b) $-(C_1-C_5)$ linear or branched alkyl optionally substituted with halogen, and

(c) phenyl optionally substituted with halogen;

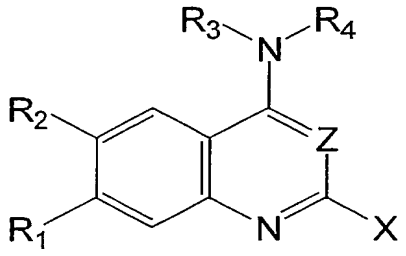
n, m and p are independently an integer from 0 - 3;

y is an integer from 0 - 2; and

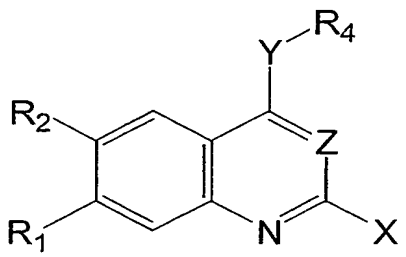
y + (m + p) equals an integer from 1 - 8;

or a purified stereoisomer or stereoisomer mixture of said compound or a salt of said compound or purified stereoisomer or stereoisomer mixture thereof.

3. A compound of the formula:



or



(I) (II)

wherein

Z is CH or N;

Y is O or S;

X is $OR_5$ or $NR_5R_6$;

$R_1$ and $R_2$ are independently selected from the group consisting of hydrogen and $-OCH_3$ wherein at least one of $R_1$ and $R_2$ is $-OCH_3$;

$R_3$ is hydrogen;

$R_4$ is $-(CH_2)_y-R_4'$ wherein:

$R_4'$ is selected from the group consisting of:

(a) $-(C_1-C_5)$ linear or branched alkyl which is optionally substituted with one to three substituents selected from the group consisting of:

(1) cyano,

(2) halogen,

(3) hydroxy,

(4) nitro,

(5) $-(C_1-C_5)$ linear or branched alkyl optionally substituted by halogen,

(6) $-(C_1-C_5)$ alkoxy,

(7) $-C(=O)R_7$,

(8) $-C(=O)OR_7$,

(9) $-C(=O)NR_8R_9$,

(10) $-S(=O)R_{10}$, and

(11) $-S(=O)_2R_{10}$,

(b) $-(C_3-C_8)$ cycloalkyl,

(c) $-(C_6-C_{10})$ aryl,

wherein (b) and (c) are optionally substituted with one to three substituents selected from the group consisting of

(1) amino,

(2) cyano,

(3) halogen,

(4) hydroxy,

(5) nitro,

(6) oxo,

(7) $-(C_1-C_5)$ linear or branched haloalkyl

(8) $-(C_1-C_5)$ haloalkoxy,

(9) $-(CH_2)_nC(=O)R_7$,

(10) $-(CH_2)_nC(=O)OR_7$,

(11) $-(CH_2)_nC(=O)C(=O)-OR_7$

(12) $-(CH_2)_nC(=O)NR_8R_9$,

(13) $-S(=O)R_{10}$,

(14) $-S(=O)_2R_{10}$;

(15) $-C(=N-R_{10})-(C_1-C_5)$ alkyl, and

(16) a saturated or unsaturated four to six membered heterocyclic ring containing one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur wherein said ring contains at least one carbon atom,

and

(d) a saturated or fully unsaturated four to eight membered heterocyclic ring containing one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring contains at least one carbon atom and wherein said ring is optionally

substituted with one to three substituents selected from the group consisting of amino, cyano, halogen, hydroxy, nitro, oxo, -($C_1$-$C_5$) alkoxy, -$(CH_2)_nC(=O)OR_7$, -$(CH_2)_nC(=O)NR_8R_9$, -$S(=O)R_{10}$, -$S(=O)_2R_{10}$ and -($C_1$-$C_5$) linear or branched alkyl optionally substituted by halogen;

or

$R_3$ and $R_4$ form, together with the nitrogen to which they are attached, a saturated or fully unsaturated four to eight membered heterocyclic ring, wherein the nitrogen is the only heteroatom, which is optionally substituted with one to three substituents selected from the group consisting of amino, cyano, halogen, hydroxy, nitro, oxo, -($C_6$-$C_{10}$)-aryl, -$C(=O)R_7$, -$(CH_2)_nC(=O)OR_7$, -$(CH_2)_nC(=O)NR_8R_9$, -$S(=O)R_{10}$, -$S(=O)_2R_{10}$ and -($C_1$-$C_5$) linear or branched alkyl optionally substituted by halogen;

$R_5$ has the formula:

-$(CH_2)_p$-O-A where A is selected from the group consisting of:

(a) hydrogen,

(b) -($C_1$-$C_5$) linear or branched alkyl, optionally substituted with cyano, halogen, hydroxy, -($C_1$-$C_5$) alkoxy- or -$NR_8R_9$, and

(c) -($C_3$-$C_8$) cycloalkyl, optionally substituted with cyano, halogen, hydroxy, -($C_1$-$C_5$)-alkyl, -($C_1$-$C_5$) alkoxy or -$NR_8R_9$;

(d) -($C_6$-$C_{10}$)-aryl, optionally substituted with one to three substituents selected from the group consisting of:

(1) cyano,

(2) halogen,

(3) hydroxy,

(4) nitro,

(5) -$NR_8R_9$,

(6) -($C_1$-$C_5$)-alkyl optionally substituted with halogen,

(7) ($C_1$-$C_5$)-alkoxy wherein the alkyl is optionally substituted with -$NR_8R_9$ or halogen,

(8) -($C_6$-$C_{10}$)-aryl-($C_1$-$C_5$) alkoxy

(9) -($C_6$-$C_{10}$)-aryloxy optionally substituted with halogen,

(10) -($C_6$-$C_{10}$)-aryl optionally substituted with halogen,

(11) -$CH_2$-($C_6$-$C_{10}$)-aryl,

(12) -C(=O)$R_7$,

(13) -C(=O)O$R_7$,

(14) -C(=O)N$R_8R_9$,

(15) -S(=O)$R_{10}$;

(16) -S(=O)$_2R_{10}$; and

(17) a saturated or fully unsaturated four to eight membered heterocyclic ring containing one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring:

(a17) contains at least one carbon atom;

(b17) is directly linked to the -($C_6$-$C_{10}$)-aryl or is linked to the -($C_6$-$C_{10}$)-aryl via an -O- linkage, and

(c17) is optionally substituted with -($C_1$-$C_5$)-alkyl, -($CH_2$)$_n$COO$R_7$ or -($CH_2$)$_n$CON$R_8R_9$,

(e) a saturated or fully unsaturated four to eight membered heterocyclic ring containing one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring contains at least one carbon atom, and is optionally substituted with

(1) -($C_1$-$C_5$) alkyl optionally substituted by halogen,

(2) -($C_6$-$C_{10}$)-aryl optionally substituted by halogen,

(3) -($C_1$-$C_5$)-alkoxy wherein the alkyl is optionally substituted with halogen,

(4) -($C_1$-$C_5$)-aryloxy wherein the aryl is optionally substituted with halogen, or

(5) oxo,

and

(f) a fused bicyclo ring wherein one ring is a saturated or fully unsaturated five to six membered heterocyclic ring which contains one to three heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said heterocyclic ring contains at least one carbon and the other ring is a saturated or fully unsaturated five to eight membered carbocycle,

or

$-(CH_2)_m$-A where A is selected from the group consisting of:

(a) hydrogen,

(b) $-(C_1-C_5)$ linear or branched alkyl optionally substituted with cyano, halogen, hydroxy, $-(C_1-C_5)$ alkoxy or $-NR_8R_9$,

(c) $-(C_3-C_8)$ cycloalkyl optionally substituted with cyano, halogen, hydroxy, $-(C_1-C_5)$-alkyl, $-(C_1-C_5)$ alkoxy or $-NR_8R_9$,

(d) $-(C_6-C_{10})$ aryl, optionally substituted with one to three substituents selected from the group consisting of:

(1) cyano,

(2) halogen,

(3) hydroxy,

(4) nitro,

(5) $-NR_8R_9$,

(6) $-(C_1-C_5)$ alkyl optionally substituted with halogen,

(7) $-(C_1-C_5)$ alkoxy wherein the alkyl is optionally substituted with $-NR_8R_9$ or halogen,

(8) $-C(=O)R_7$,

(9) $-C(=O)OR_7$,

(10) $-C(=O)NR_8R_9$,

(11) $-S(=O)R_{10}$;

(12) $-S(=O)_2R_{10}$; and

(13) a saturated or fully unsaturated four to eight membered heterocyclic ring containing one to four heteroatoms

selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring:

(a13) contains at least one carbon atom;

(b13) is directly linked to the -($C_6$-$C_{10}$) aryl or is linked to the -($C_6$-$C_{10}$) aryl via an -O- linkage, and

(c13) is optionally substituted with -($C_1$-$C_5$)-alkyl, -$(CH_2)_nC(=O)OR_7$ or -$(CH_2)_nC(=O)NR_8R_9$,

(e) a saturated or fully unsaturated four to eight membered heterocyclic ring containing one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring contains at least one carbon atom, and is optionally substituted with

(1) -($C_1$-$C_5$)-alkyl optionally substituted by halogen,

(2) phenyl optionally substituted by halogen,

(3) -($C_1$-$C_5$)-alkoxy wherein the alkyl is optionally substituted with halogen,

(4) -($C_1$-$C_5$)-aryloxy wherein the aryl is optionally substituted with halogen, or

(5) oxo,

and

(f) a fused bicyclo ring wherein one ring is a saturated or fully unsaturated five to six membered heterocyclic ring which contains one to three heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said heterocyclic ring contains at least one carbon atom and the other ring is a saturated or fully unsaturated five to eight membered carbocycle;

$R_6$ is selected from the group consisting of:

(a) hydrogen, and

(b) -($C_1$-$C_5$) linear or branched alkyl,

wherein $R_5$ and $R_6$ are not both hydrogen;

or

$R_5$ and $R_6$ form, together with the nitrogen to which they are attached, a saturated or fully unsaturated four to eight membered heterocyclic ring, which optionally contains one to three additional heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur wherein said ring contains at least one carbon atom, and wherein said ring is optionally substituted with one to three substituents selected from the group consisting of:

(a) amino,

(b) cyano,

(c) halogen,

(d) hydroxy,

(e) nitro,

(f) oxo,

(g) -($C_1$-$C_5$) linear or branched alkyl optionally substituted by halogen or -($C_1$-$C_5$) alkoxy,

(j) -($C_6$-$C_{10}$)-aryl optionally substituted by halogen or -($C_1$-$C_5$)-alkyl,

(k) -($C_1$-$C_5$)-alkyl-phenyl optionally substituted by halogen or -($C_1$-$C_5$) alkyl,

(l) $-(CH_2)_nCOOR_7$,

(m) $-(CH_2)_nCONR_8R_9$,

(n) $-(CH_2)_nNR_8R_9$,

(o) $-S(=O)R_{10}$,

(p) $-S(=O)_2R_{10}$, and

(q) -($CH_2$)$_n$-Q, wherein Q is:

(q1) a four to eight membered saturated or fully unsaturated heterocyclic ring containing one to four nitrogens, wherein said ring contains at least one carbon atom, or

(q2) -$C_6$-$C_{10}$-aryl optionally substituted with halogen or -($C_1$-$C_5$) alkyl;

wherein,

(i) $R_3 \neq R_4$,

(ii) $R_5 \neq R_6$, and

(iii) ($R_3$ and $R_4$) $\neq$ ($R_5$ and $R_6$)

$R_7$ is selected from the group consisting of hydrogen, -($C_1$-$C_5$) linear or branched alkyl, phenyl, -($C_1$-$C_5$)-alkyl-phenyl, and ($C_3$-$C_{10}$) cycloalkyl which are optionally substituted with one to three substituents selected from the group consisting of halogen, oxo, -($C_1$-$C_5$) alkoxy, $-(CH_2)_nC(=O)R_{11}$, $-(CH_2)_nC(=O)OR_{11}$, $-(CH_2)_nC(=O)NR_8R_9$, $-S(=O)R_{10}$, $-S(=O)_2R_{10}$ and -($C_1$-$C_5$) linear or branched alkyl optionally substituted by halogen;

$R_8$ and $R_9$ are independently selected from the group consisting of hydrogen, -($C_1$-$C_5$) linear or branched alkyl, -($C_1$-$C_5$) alkoxy or –($C_6$-$C_{10}$) aryl which is optionally substituted with one to three substituents selected from the group consisting of halogen, -($C_1$-$C_5$) alkoxy, -($C_1$-$C_5$) alkylamino, $-(CH_2)_nC(=O)R_7$, $-(CH_2)_nC(=O)OR_7$, $-(CH_2)_nC(=O)NR_8R_9$, $-S(=O)R_{10}$, $-S(=O)_2R_{10}$ and -($C_1$-$C_5$) linear or branched alkyl optionally substituted by halogen; or

$R_8$ and $R_9$ form, together with the nitrogen to which they are attached, a saturated or fully unsaturated, four to eight membered heterocyclic ring, wherein said ring has one to three additional heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur wherein said ring contains at least one carbon atom and wherein said heterocyclic ring is optionally substituted with -($C_1$-$C_5$) linear or branched alkyl;

$R_{10}$ is hydrogen, $-NR_8R_9$, $-OR_{11}$, -($C_1$-$C_5$) linear or branched alkyl, or phenyl;

$R_{11}$ is hydrogen, -($C_1$-$C_5$) linear or branched alkyl, or phenyl;

n, m and p are independently an integer from 0 - 3; and

y is an integer from 0 - 2,

or a purified stereoisomer or stereoisomer mixture of said compound or a salt of said compound or purified stereoisomer or stereoisomer mixture thereof.

4. A pharmaceutical composition for the inhibition of prolyl peptidase or the induction of apoptosis which comprises a therapeutically effective amount of one or more compounds of any one of claims 1 - 3 and a pharmaceutically acceptable excipient.

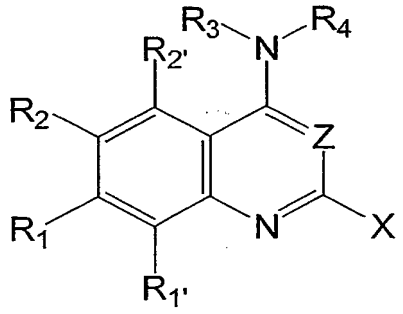
5. The pharmaceutical composition of claim 4 which further comprises an additional agent selected from the group consisting of agent(s) which induce apoptosis, anti-proliferative agent(s) and mixtures thereof.

6. The pharmaceutical composition of claim 5 wherein the agent(s) which induce apoptosis is selected from the group consisting of A23187, N-Acetyl-L-cysteine, actinomycin D, tyrphostin A9, tyrphostin A25, AG 490, AG 1714, anandamide, anisomycin, aphidicolin, bafilomycin A1, berberine hemisulfate, betulinic acid, bleomycin sulfate, CAFdA, calphostin C, camptothecin, CAPE, chelerythrine chloride, 2-chloro-2'-deoxyadenosine, 2-chloro-2'-deoxyadenosine 5'-triphosphate, colcemid, cochicine, corticosterone, cycloheximide, cyclophosphamide monohydrate, cyclosporine A, daunorubicin hydrocloride, dexamethasone, 3,3'-diindolylmethane, dolastatin 15, doxorubicin hydrochloride, erbstatin analog, ET-18-$OCH_3$, etoposide, etoposide phosphate, 5-fluorouracil, folimycin, forskolin, genistein, glycodeoxycholic acid sodium salt, H-7 dihydrochloride, H-89 dihydrochloride, harringtonine, homoharringtonine, 4-hydroxynonenal, 4-hydroxyphenylretinamide, hydroxyurea, indanocine, ionomycin free acid, ionomycin calcium salt, KN-93, methotrexate, mitomycin C, okadaic acid, oligomycin, p53 activator, paclitaxel, phorbol-12-myristate-13-acetate, (pivaloyloxy)methyl butyrate, puromycin dihydrochloride, 1-pyrrolidinecarbodithioic acid ammonium salt, quercetin dihydrate, rapamycin, SNAP, SNOG, sodium butyrate, sodium 4-phenylbutyrate, spermine tetrachloride, D-*erythro*-sphingosine (free base; N-Acetyl-; N,N-dimethyl-; N-hexanoyl-; and N-octanoyl forms), stautosporine, sulfasalizine,

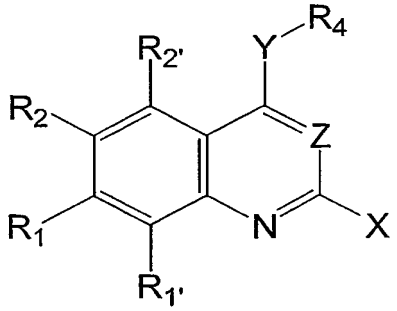
sulindac, tamoxifen citrate, 4-hydroxy-(Z)-tamoxifen, thapsigargin, α-toxin, TRAIL, valinomycin, (±)-verapamil hydrochloride, veratridine and vitamin E succinate.

7. The pharmaceutical composition of claim 5 wherein the anti-proliferative agent(s) is selected from the group consisting of asparaginase, bleomycin, carboplatin, carmustine, chlorambucil, cisplatin, colaspase, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, daunorubicin, doxorubicin (adriamycine), epirubicin, etoposide, 5-fluorouracil, hexamethylmelamine, hydroxyurea, ifosfamide, irinotecan, leucovorin, lomustine, mechlorethamine, 6-mercaptopurine, mesna, methotrexate, mitomycin C, mitoxantrone, prednisolone, prednisone, procarbazine, raloxifen, streptozocin, tamoxifen, thioguanine, topotecan, vinblastine, vincristine, vindesine, aminoglutethimide, L-asparaginase, azathioprine, 5-azacytidine cladribine, busulfan, diethylstilbestrol, 2', 2'-difluorodeoxycytidine, docetaxel, erythrohydroxynonyladenine, ethinyl estradiol, 5-fluorodeoxyuridine, 5-fluorodeoxyuridine monophosphate, fludarabine phosphate, fluoxymesterone, flutamide, hydroxyprogesterone caproate, idarubicin, interferon, medroxyprogesterone acetate, megestrol acetate, melphalan, mitotane, paclitaxel, pentostatin, N-phosphonoacetyl-L-aspartate (PALA), plicamycin, semustine, teniposide, testosterone propionate, thiotepa, trimethylmelamine, uridine, vinorelbine and epothilone.

8. A method of treatment wherein said treatment is selected from the group consisting of the inhibiting prolylpeptidase, inducing apoptosis and treating cancer, for a patient in need thereof, which comprises administering a therapeutically effective amount of a compound of the formula:




or




(Ia) (IIa)

wherein,

Z is CH or N;

Y is O or S;

X is $OR_5$ or $NR_5R_6$;

$R_1$, $R_{1'}$, $R_2$ and $R_{2'}$ are independently selected from the group consisting of hydrogen, amino, cyano, halogen, hydroxy, methoxy and nitro;

$R_3$ is selected from the group consisting of:

(a) hydrogen, and

(b) -$C_1$-$C_{10}$ linear or branched alkyl,

$R_4$ is -$(CH_2)_y$-$R_4$' wherein:

$R_4$' is selected from the group consisting of:

(a) -$C_1$-$C_5$ linear or branched alkyl which is optionally substituted with one to three substituents selected from the group consisting of:

(1) cyano,

(2) halogen,

(3) hydroxy,

(4) nitro,

(5) -$C_1$-$C_5$ linear or branched alkyl optionally substituted by halogen,

(6) $C_1$-$C_5$ alkoxy-,

(7) -C(=O)$R_7$,

(8) -C(=O)$OR_7$,

(9) -C(=O)$NR_8R_9$,

(10) -S(=O)$R_{10}$, and

(11) -$S(=O)_2R_{10}$;

(b) -$C_3$-$C_8$ cycloalkyl,

(c) -$C_6$-$C_{10}$ aryl,

wherein (b) and (c) are optionally substituted with one to three substituents selected from the group consisting of

(1) amino,
(2) cyano,
(3) halogen,
(4) hydroxy,
(5) nitro,
(6) oxo,
(7) -$C_1$-$C_5$ linear or branched alkyl optionally substituted by halogen or hydroxy,
(8) $C_1$-$C_5$ haloalkoxy-,
(9) -$(CH_2)_nC(=O)R_7$,
(10) -$(CH_2)_nC(=O)OR_7$,
(11) -$(CH_2)_nC(=O)C(=O)$-$OR_7$,
(12) -$(CH_2)_nC(=O)NR_8R_9$,
(13) -$S(=O)R_{10}$ ,
(14) -$S(=O)_2R_{10}$,
(15) -$C(=N$-$R_{10})$-$C_1$-$C_5$-alkyl, and
(16) a saturated or unsaturated four to six membered heterocyclic ring containing one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring contains at least one carbon atom,

and

(d) a saturated or unsaturated four to six membered heterocyclic ring containing one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring contains at least one carbon atom and wherein said ring is optionally substituted with one to three substituents selected from the group consisting of amino, cyano, halogen, hydroxy, nitro, oxo, $C_1$-$C_5$-alkoxy-, -$(CH_2)_nC(=O)OR_7$, -$(CH_2)_nC(=O)NR_8R_9$, -$S(=O)R_{10}$, -$S(=O)_2R_{10}$ and -$C_1$-$C_5$ linear or branched alkyl optionally substituted by halogen;

or

$R_3$ and $R_4$ form, together with the nitrogen to which they are attached, a saturated or unsaturated, four to eight membered heterocyclic ring, wherein the nitrogen is the only heteroatom, which is optionally substituted with one to three substituents selected from the group consisting of amino, cyano, halogen, hydroxy, nitro, oxo, $C_1$-$C_5$ alkoxy-, phenyl, $-C(=O)R_7$, $-(CH_2)_nC(=O)OR_7$, $-(CH_2)_nC(=O)NR_8R_9$, $-S(=O)R_{10}$, $-S(=O)_2R_{10}$ and $-C_1$-$C_5$ linear or branched alkyl optionally substituted by halogen;

$R_5$ has the formula $(CHR_{11})_m$-A or $(CHR_{11})_p$-O-A, where A is selected from the group consisting of:

(a) hydrogen,

(b) $-C_1$-$C_5$ linear or branched alkyl optionally substituted with cyano, halogen, hydroxy, $C_1$-$C_5$ alkoxy- or $-NR_8R_9$,

(c) $-C_3$-$C_8$ cycloalkyl optionally substituted with cyano, halogen, hydroxy, $-C_1$-$C_5$-alkyl, $C_1$-$C_5$ alkoxy- or $-NR_8R_9$,

(d) $-C_6$-$C_{10}$ aryl optionally substituted with one to three substituents selected from the group consisting of:

(1) cyano,

(2) halogen,

(3) hydroxy,

(4) nitro,

(5) $-NR_8R_9$,

(6) $-C_1$-$C_5$ linear or branched alkyl optionally substituted with $-NR_8R_9$ or halogen,

(7) $C_1$-$C_5$-alkoxy- wherein the alkyl is optionally substituted with $-NR_8R_9$ or halogen,

(8) $C_6$-$C_{10}$-aryl-$C_1$-$C_5$-alkoxy-

(9) $C_6$-$C_{10}$-aryloxy- optionally substituted with halogen,

(10) $-C_6$-$C_{10}$-aryl optionally substituted with halogen,

(11) $-CH_2$-$C_6$-$C_{10}$-aryl,

(12) $-C(=O)R_7$,

(13) $-C(=O)OR_7$,

(14) $-C(=O)NR_8R_9$,

(15) $-S(=O)R_{10}$,

(16) $-S(=O)_2R_{10}$, and

(17) a saturated or unsaturated four to eight membered heterocyclic ring containing one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring:

(a17) contains at least one carbon atom;

(b17) is directly linked to the $-C_6$-$C_{10}$-aryl or is linked to the $-C_6$-$C_{10}$-aryl via an -O- linkage; and

(c17) is optionally substituted with $-C_1$-$C_5$-alkyl, $-(CH_2)_nC(=O)OR_7$ or $-(CH_2)_nC(=O)NR_8R_9$,

(e) a saturated or unsaturated four to eight membered heterocyclic ring containing one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring contains at least one carbon atom, and is optionally substituted with

(1) $C_1$-$C_5$-alkyl optionally substituted by halogen,

(2) phenyl optionally substituted by halogen,

(3) $C_1$-$C_5$-alkoxy- wherein the alkyl is optionally substituted with halogen,

(4) $C_6$-$C_{10}$-aryloxy- wherein the aryl is optionally substituted with halogen, or

(5) oxo;

(f) a fused bicyclo ring wherein one ring is a saturated or unsaturated five to six membered saturated or unsaturated heterocyclic ring which contains one to three heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said heterocyclic ring contains at least one carbon atom, and the other ring is a saturated or unsaturated five to eight membered carbocyclic ring,

and

(g) a fused bicyclo ring wherein each ring is independently a saturated or unsaturated five to eight membered carbocyclic ring;

$R_6$ is selected from the group consisting of:

(a) hydrogen, and

(b) $C_1$-$C_5$ linear or branched alkyl;

wherein $R_5$ and $R_6$ are not both hydrogen;

or

$R_5$ and $R_6$ form, together with the nitrogen to which they are attached, a saturated or unsaturated four to eight membered heterocyclic ring, which optionally contains one to three additional nitrogen atoms wherein said ring contains at least one carbon atom, and wherein said ring is optionally substituted with one to three substituents selected from the group consisting of:

(a) amino,

(b) cyano,

(c) halogen,

(d) hydroxy,

(e) nitro,

(f) oxo,

(g) -$C_1$-$C_5$ linear or branched alkyl optionally substituted by halogen or $C_1$-$C_5$-alkoxy-,

(h) $C_1$-$C_5$ alkoxy-,

(i) -$C_1$-$C_5$ alkoxy-$C_1$-$C_5$-alkyl,

(j) -$C_6$-$C_{10}$-aryl optionally substituted by halogen or -$C_1$-$C_5$-alkyl,

(k) -$C_1$-$C_5$-alkyl-phenyl optionally substituted by halogen or -$C_1$-$C_5$-alkyl,

(l) -$(CH_2)_nCOOR_7$,

(m) -$(CH_2)_nCONR_8R_9$,

(n) -$(CH_2)_nNR_8R_9$,

(o) -$S(=O)R_{10}$,

(p) $-S(=O)_2R_{10}$, and

(q) $-(CH_2)_n-Q$, wherein Q is:

(q1) a four to eight membered saturated or unsaturated heterocyclic ring containing one to four nitrogens, wherein said ring contains at least one carbon atom, or

(q2) $-C_6-C_{10}$-aryl optionally substituted with halogen or $-C_1-C_5$-alkyl;

$R_7$ is selected from the group consisting of hydrogen, $-C_1-C_5$ linear or branched alkyl, phenyl, $-C_1-C_5$-alkyl-phenyl, and $-C_3-C_{10}$ cycloalkyl which are optionally substituted with one to three substituents selected from the group consisting of halogen, oxo, $C_1-C_5$ alkoxy-, $-C(=O)R_7$ $-(CH_2)_nC(=O)OR_7$, $-(CH_2)_nC(=O)NR_8R_9$, $-S(=O)R_{10}$, $-S(=O)_2R_{10}$ and $-C_1-C_5$ linear or branched alkyl optionally substituted by halogen;

$R_8$ and $R_9$ are independently selected from the group consisting of:

(a) hydrogen,

(b) $-C_1-C_5$ linear or branched alkyl which is optionally substituted with a substituent selected from the group consisting of halogen and $C_1-C_5$ alkoxy-,

(c) $C_1-C_5$ alkoxy-,

(d) $-C_6-C_{10}$ aryl, and

(e) $-(CH_2)_n-R$ wherein R is a saturated or unsaturated five to six membered heterocyclic ring containing one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring contains at least one carbon atom,

wherein (c)-(e) are optionally substituted with one to three substituents selected from the group consisting of halogen, $-C_1-C_5$ alkylamino, $C_1-C_5$ alkoxy-, $-C(=O)R_7$, $-(CH_2)_nC(=O)OR_7$, $-(CH_2)_nC(=O)NR_8R_9$, $-S(=O)R_{10}$, $-S(=O)_2R_{10}$ and $-C_1-C_5$ linear or branched alkyl optionally substituted by halogen,

or

$R_8$ and $R_9$ form, together with the nitrogen to which they are attached, a saturated or unsaturated four to eight membered heterocyclic ring, optionally containing one to three additional heteroatoms selected from the group consisting of nitrogen and oxygen, wherein said ring contains at least one carbon atom and wherein said heterocyclic ring is optionally substituted with -$C_1$-$C_5$ linear or branched alkyl;

$R_{10}$ is hydrogen, -$NR_8R_9$, -$OR_{11}$, -$C_1$-$C_5$ linear or branched alkyl, or phenyl;

each occurrence of $R_{11}$ is independently selected from the group consisting of hydrogen, -$C_1$-$C_5$ linear or branched alkyl and phenyl;

n, m and p are independently an integer from 0 - 3;

y is an integer from 0 - 2;

or a purified stereoisomer or stereoisomer mixture of said compound or a salt of said compound or purified stereoisomer or stereoisomer mixture thereof.

9. The method of inducing apoptosis of claim 8 wherein said composition further comprises an additional agent selected from the group consisting of prolylpeptidase inhibitors, apoptosis inducers, anti-proliferative agent(s) and mixtures thereof.

10. The method of claim 9 wherein the anti-proliferative agent(s) is selected from the group consisting of A23187, N-Acetyl-L-cysteine, actinomycin D, tyrphostin A9, tyrphostin A25, AG 490, AG 1714, anandamide, anisomycin, aphidicolin, bafilomycin A1, berberine hemisulfate, betulinic acid, bleomycin sulfate, CAFdA, calphostin C, camptothecin, CAPE, chelerythrine chloride, 2-chloro-2'-deoxyadenosine, 2-chloro-2'-deoxyadenosine 5'-triphosphate, colcemid, cochicine, corticosterone, cycloheximide, cyclophosphamide monohydrate, cyclosporine A, daunorubicin hydrocloride, dexamethasone, 3,3'-diindolylmethane, dolastatin 15, doxorubicin hydrochloride, erbstatin analog, ET-18-$OCH_3$, etoposide, etoposide phosphate, 5-fluorouracil, folimycin, forskolin, genistein, glycodeoxycholic acid

sodium salt, H-7 dihydrochloride, H-89 dihydrochloride, harringtonine, homoharringtonine, 4-hydroxynonenal, 4-hydroxyphenylretinamide, hydroxyurea, indanocine, ionomycin free acid, ionomycin calcium salt, KN-93, methotrexate, mitomycin C, okadaic acid, oligomycin, p53 activator, paclitaxel, phorbol-12-myristate-13-acetate, (pivaloyloxy)methyl butyrate, puromycin dihydrochloride, 1-pyrrolidinecarbodithioic acid ammonium salt, quercetin dihydrate, rapamycin, SNAP, SNOG, sodium butyrate, sodium 4-phenylbutyrate, spermine tetrachloride, D-*erythro*-sphingosine (free base; N-Acetyl-; N,N-dimethyl-; N-hexanoyl-; and N-octanoyl forms), stautosporine, sulfasalizine, sulindac, tamoxifen citrate, 4-hydroxy-(Z)-tamoxifen, thapsigargin, α-toxin, TRAIL, valinomycin, (±)-verapamil hydrochloride, veratridine, vitamin E succinate and mixtures thereof.

11. The method of claim 9 wherein wherein the anti-proliferative agent(s) is selected from the group consisting of asparaginase, bleomycin, carboplatin, carmustine, chlorambucil, cisplatin, colaspase, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, daunorubicin, doxorubicin (adriamycine), epirubicin, etoposide, 5-fluorouracil, hexamethylmelamine, hydroxyurea, ifosfamide, irinotecan, leucovorin, lomustine, mechlorethamine, 6-mercaptopurine, mesna, methotrexate, mitomycin C, mitoxantrone, prednisolone, prednisone, procarbazine, raloxifen, streptozocin, tamoxifen, thioguanine, topotecan, vinblastine, vincristine, vindesine, aminoglutethimide, L-asparaginase, azathioprine, 5-azacytidine cladribine, busulfan, diethylstilbestrol, 2', 2'-difluorodeoxycytidine, docetaxel, erythrohydroxynonyladenine, ethinyl estradiol, 5-fluorodeoxyuridine, 5-fluorodeoxyuridine monophosphate, fludarabine phosphate, fluoxymesterone, flutamide, hydroxyprogesterone caproate, idarubicin, interferon, medroxyprogesterone acetate, megestrol acetate, melphalan, mitotane, paclitaxel, pentostatin, N-phosphonoacetyl-L-aspartate (PALA), plicamycin, semustine, teniposide, testosterone propionate, thiotepa, trimethylmelamine, uridine, vinorelbine and epothilone.

12. The method of claim 8 wherein said treatment is inhibiting prolylpeptidase.

13. The method of claim 8 wherein said treatment is inducing apoptosis.

14. The method of claim 8 wherein said treatment is the treatment of cancer.

# INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/41176

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D239/95 C07D401/04 C07D409/12 C07D413/14 C07D417/12
C07D403/12 C07D407/12 C07D409/14 C07D413/12 C07D401/12
A61K31/505 A61K31/47 C07D215/22 C07D215/38 C07D215/42

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, CHEM ABS Data, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| E | WO 03 018561 A (ASTRAZENECA AB ;D AMICO DERIN (US)) 6 March 2003 (2003-03-06) examples 17-23,26,30;24,25,32-34 --- | 1,3 |
| E | WO 03 018560 A (ASTRAZENECA AB ;D AMICO DERIN (US)) 6 March 2003 (2003-03-06) examples 5,6,21,23-26;22,31,32 --- | 1,3 |
| X,P | WO 02 076975 A (AVENTIS PHARMA SA) 3 October 2002 (2002-10-03) examples page 88,lines 10-11; page 99,lines 25-26 --- | 1-14 |
| X,P | WO 02 50066 A (PIERARD FRANCOISE ;GOLEC JULIAN (GB); BEBBINGTON DAVID (GB); CHARR) 27 June 2002 (2002-06-27) page 51 --- -/-- | 8-14 |

[X] Further documents are listed in the continuation of box C.

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| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 15 May 2003 | 02/06/2003 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL – 2280 HV Rijswijk<br>Tel. (+31–70) 340–2040, Tx. 31 651 epo nl,<br>Fax: (+31–70) 340–3016 | Frelon, D |

Form PCT/ISA/210 (second sheet) (July 1992)

# INTERNATIONAL SEARCH REPORT

[redacted]national Application No
PCT/US 02/41176

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 //(C07D401/04,239:00,211:00),(C07D409/12,333:00,239:00),
(C07D413/14,333:00,273:00,239:00),(C07D417/12,277:00,239:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
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| X,P | WO 02 26713 A (KING S COLLEGE LONDON ;WHITFIELD PHILIP JOHN (GB); JONES KEITH (GB) 4 April 2002 (2002-04-04) examples 37,39,58 --- | 1 |

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlyihg the invention

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| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 15 May 2003 | |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1,4-14(partially)

   Compounds of formulas (I) and (II) defined as in claim 1

2. Claims: 2,4-14(partially)

   Compounds of formulas (I) and (II) defined as in claim 2

3. Claims: 3,4-14(partially)

   Compounds of formulas (I) and (II) as defined in claim 3

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**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 8 to 14 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [X] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

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